Pediatrics

VOLUME 2 OCTOBER, 1948 NUMBER 4

ORIGINAL ARTICLES

REPRODUCTIVE HISTORIES OF THE MOTHERS OF 322 INFANTS WITH ERYTHROBLASTOSIS

By EDITH L. POTTER, M.D.
Chicago, Ill.

IN CONNECTION with studies of erythroblastosis fetalis conducted at the Chicago Lying-in Hospital between January 1, 1935 and January 1, 1948 reproductive histories have been obtained for 175 Rh-negative women* who have given birth to one or more infants proven to have had this disease. Of these women, 111 delivered at least one affected child in this hospital. The children of six were delivered elsewhere and admitted to the Bobs Roberts Hospital soon after birth. The diagnosis was made on the children of 35 women, the dead infants having been sent to the Chicago Lying-in Hospital for postmortem examination. Twenty-six additional women were studied after having given birth elsewhere to a child with erythroblastosis, the diagnosis having been adequately corroborated in each case. Observed during the course of these studies but not included in the present report were 15 infants with erythroblastosis for whom maternal histories and Rh determinations could not be obtained.

The 175 women included in the present study have delivered 699 fetuses and infants. These include 341 delivered before the birth of the first infant with erythroblastosis, 179 born in the pregnancies producing the first erythroblastotic infants, and 179 born in subsequent pregnancies. Twins were delivered to two women in pregnancies before the diagnosis was made, to four in the pregnancy in which it was first made and to one in a subsequent pregnancy.

PREGNANCIES ANTEDATING THE BIRTH OF AN INFANT WITH ERYTHROBLASTOSIS

Only seven women gave no history of a pregnancy prior to the birth of an erythroblastotic infant. Four of these had received multiple transfusions before becoming pregnant. Two of the remaining three were illegitimately pregnant and there is good reason

From the Department of Obstetrics and Gynecology, The University of Chicago and the Chicago Lying-in Hospital.

(Received for publication June 6, 1948.)

* One of the patients included in this group was Rh-positive and was immunized to Hr′.

to believe the histories may not be accurate. These three in whom no condition was found which might have lead to immunization prior to the pregnancy ending in the birth of an affected child make up only 1.7% of the total number of women. In 98.3% a pregnancy or transfusion were possible causes of the immunization which resulted in the birth of an infant with erythroblastosis in a subsequent pregnancy. Five of the seven erythroblastotic infants delivered by the women with no earlier pregnancies survived.

Only 12 additional women had no living children at the time the first infant with erythroblastosis was born. These 12 pregnancies ended in the delivery of two infants who survived, five who were stillborn and five who died. Of the two women whose children survived, one had lost an infant from intracranial hemorrhage and the other lost one from anoxia associated with a prolapsed cord and had had a subsequent abortion. The five women whose children died of erythroblastosis included three who had had one or more induced abortions, one who had lost a child from anoxia associated with placenta previa and one who had lost two children, one from a malformation and one from prematurity. Of the five women whose children were stillborn, two had had one or more abortions, one had had two abortions and a child who died as a result of placenta previa, one had had a child die from intracranial hemorrhage and twins die from prematurity, and one had lost a child from intracranial hemorrhage.

The seven women without earlier pregnancies and the 12 women whose earlier pregnancies had ended unsuccessfully make a total of 19 who had no children living when the first infant with erythroblastosis was born. Seven of these infants with erythroblastosis survived. Consequently only 12(7%) of the entire group of women are childless.

The 341 pregnancies occurring before the appearance of erythroblastosis resulted in the birth of 256 children who survived, seven who were stillborn, 13 who died after birth, and 65 fetuses who were aborted. Ten of the deaths and stillbirths occurred in the offspring of women who had no surviving children at the birth of the first erythroblastotic infant. The birth of a normal infant intervened between the pregnancy ending unsuccessfully and the one in which erythroblastosis appeared in the other 10. In 19 women one or more abortions (21) were followed by the birth of a normal child and in 32 women 44 abortions were found either as the only pregnancies (5) or intervening between the birth of the last normal child and the first with erythroblastosis (27).

The number of unsuccessful pregnancies in the total group of 175 women is abnormally high. Only 75% of the recorded pregnancies ended successfully; 19% ended in abortion and 6% in stillbirth or neonatal death.

In order to compare these figures with those existing for women not immunized to Rh, reproductive histories were summarized for a group of patients delivered in 1947. Twenty-four hundred and ten consecutively discharged patients, each of whom had had fewer than six pregnancies and none of whom gave birth to an infant with erythroblastosis, were included in this control series.

Only three patients had had more than five pregnancies preceding the first birth of an infant with erythroblastosis and it was felt a better comparison of the outcome of a similar number of pregnancies could be obtained by omitting women with more than five pregnancies from both groups. The seven with no earlier pregnancies were omitted from the erythroblastotic group since there were none comparable in the control group. This leaves 65 women who had had one to five pregnancies before the birth of an affected infant.

Two thousand and fifty three (85.2%) of the control group were Rh-positive, 357 (14.8%) were Rh-negative. The Rh-positive group, the Rh-negative group and the group composed of mothers of erythroblastotic infants are remarkably similar in distribution of pregnancies (Table 1). Slightly fewer than half of each group had had one pregnancy, about one-third had had two and the remainder had had from three to five.

TABLE I

COMPARISON OF TOTAL PREGNANCIES IN NON-IMMUNIZED RH-POSITIVE AND RH-NEGATIVE WOMEN WITH PREGNANCIES PRECEDING THE BIRTH OF AN INFANT WITH ERYTHROBLASTOSIS IN WOMEN WHO SUBSEQUENTLY GAVE BIRTH TO AN INFANT WITH THIS DISEASE: GRAVIDA 1 THROUGH 5

	Normal Rh+ Total pregnancies	Normal Rh− Total pregnancies	Immunized Rh− pregnancies antedating birth of an infant with erythroblastosis
Total patients	2053	357	165
Total pregnancies	3965	681	320
Pregnancies per patient	1.9	1.8	1.9
Surviving infants	3562	604	243
Surviving infants per patient	1.7	1.7	1.4
Unsuccessful pregnancies	403	77	77
Abortions	295	66	58
Stillbirths	46	7	7
Deaths	62	4	12
Unsuccessful pregnancies, percent	10%	11%	24%
Unsuccessful pregnancies exclusive of abortions, percent	2.9%	1.7%	7.2%
Total women with 1 or more unsuccessful pregnancies	313	59	62
Women with 1 or more unsuccessful pregnancies, percent	15%	16%	38%
Distribution of patients in relation to number of pregnancies			
1 pregnancy	44%	45%	44%
2 pregnancies	33%	30%	32%
3 pregnancies	14%	17%	15%
4–5 pregnancies	9%	8%	9%

All groups had an average of 1.8 to 1.9 pregnancies per patient. The Rh-positive and Rh-negative control groups are similar in the proportionate number of unsuccessful pregnancies and in the average number of surviving children. Great differences are found, however, in the percentage of unsuccessful pregnancies in the control groups and in the one with subsequent erythroblastotic infants. Fewer than 11% of the pregnancies of the control groups were unsuccessful while 24% of the pre-erythroblastotic group ended in abortion, stillbirth or death. The latter group averaged only 1.4 living children in comparison to 1.7 for the control groups. In the two control groups 85% of the Rh-

positive women and 84% of the Rh-negative women had had no unsuccessful pregnancies while in the group with subsequent erythroblastotic infants only 62% had had no unsuccessful pregnancies.

Six women who had not had an unsuccessful pregnancy before giving birth to an erythroblastotic infant had been transfused with blood of unknown Rh, following the birth of the last normal child. Adding these patients decreases to 59% the number of women who had not had an abortion, stillbirth, death or transfusion before the birth of the first erythroblastotic infant.

Both the abortion rate and the total mortality rate were over twice as great among the pregnancies of women who subsequently gave birth to infants with erythroblastosis as they were in a comparable number of pregnancies in an unaffected series of women. This strongly suggests that the deaths, stillbirths or abortions or some factor associated with them contributed to the immunization which resulted in the subsequent birth of an infant with erythroblastosis, an interpretation which is especially probable in the group in which the unsuccessful pregnancy immediately preceded the first with erythroblastosis.

In 32 women one or several abortions (often induced) followed the birth of the last normal child and preceded the birth of an infant with erythroblastosis. Five women were given blood transfusions of unknown Rh because of bleeding associated with the abortion. Eight patients were given transfusions after the birth of the last normal child and four patients had been transfused but had not been pregnant. The 17 women who received transfusions had, as their first erythroblastotic infants, seven who survived the disease, four who died and six who were stillborn. Forty-four women had an abortion or a transfusion or both in the period immediately preceding the birth of an infant with erythroblastosis. It seems probable that none of the abortions were caused by maternal immunization to Rh but that in all likelihood they contributed to the subsequent immunization.

A diagnosis of erythroblastosis was not made on any of the 256 living infants; but, since few of them were observed by us and many were born before Rh testing became so widespread, it is possible that some may have had mild, self limited forms of the disease. A history of jaundice or anemia has been obtained in a few and it seems probable, particularly when later infants had a fatal form of erythroblastosis, that some of these older surviving siblings may have been affected. The number of surviving children born before the first infants with erythroblastosis is shown in relation to the fate of the first erythroblastotic infant in Table II. It is interesting that the women whose first child with erythroblastosis survived averaged slightly fewer living children before the birth of the infant with erythroblastosis than did those women whose children died or were stillborn. This is largely because they had fewer preceding pregnancies (Table III). They averaged only 1.6 preceding pregnancies in contrast to 2.3 for those whose first child with erythroblastosis was stillborn. This also suggests that the nonsurviving children may be later in birth order because they were preceded by undiagnosed affected siblings.

Pregnancy in Which the Diagnosis of Erythroblastosis Was Made for the First Time

The first erythroblastotic child born to each of these 175 women died in the neonatal period in 60 instances, before birth in 56 and survived in 62. Four of the pregnancies ended in the delivery of twins. In one instance both twins survived, in one both died,

in one instance one was stillborn and the other survived, and in one instance one died and the other was Rh-negative and normal. The place in family occupied by the infant on whom the first diagnosis of erythroblastosis was made is shown in Table II. Seventy-five percent of all women in this series who gave birth to infants with erythroblastosis delivered their first affected child before the fourth pregnancy. The place in family of the first affected child is slightly earlier among infants who survived than among those who died or were stillborn. The women whose children were first affected in later gestations had in general a greater number of preceding abortions and this fact may contribute to the appearance of the disease in later pregnancies and to its severity.

TABLE II

PREGNANCY IN WHICH DIAGNOSIS OF ERYTHROBLASTOSIS WAS FIRST MADE*

Outcome of first erythroblastic pregnancy	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	Total
Infant survived	5	25	20	9	1	1				61
Infant died	0	28	16	7	5	3				59
Infant stillborn	2	17	19	9	3	2	1	1	1	55
Total	7	70	55	25	9	6	1	1	1	175

* Abortions included.

TABLE III

NUMBER OF ERYTHROBLASTIC INFANTS PER MOTHER*

Fate of the first child suffering from erythroblastosis	1	2	3	4	5	6	7	8	Total number affected infants	Total number of mothers
First infant survived	47	11	3						78	61
First infant died	19	26	9	2	3				121	59
First infant stillborn	24	14	5	7	4	0	0	1	123	55
Total	90	51	17	9	7	0	0	1	322	175

* Abortions excluded.

The length of life of the 60 infants who died after birth was less than eight hours in 11 instances and from eight to 24 hours in seven more. Fourteen infants died on the second day, 16 on the third, 3 on the fourth, 3 on the fifth, 1 on the sixth and 1 on the sixteenth day. The exact time is unrecorded in 4. Eighty-five percent of those for whom length of life is known lived less than 72 hours. In this group only 7.5% of all infants who were born alive died if they survived the third day.

This series does not given an indication of the proportionate number of deaths and stillbirths that might be expected in a random sample of 175 erythroblastotic infants. The series has an excessive number of nonsurviving infants for two reasons: (1) The group received from other institutions for postmortem examination were all dead and

the number born during the same period who survived is unknown. (2) The disease was not recognized in living infants at the Chicago Lying-in Hospital before 1940 and the first recorded diagnosis was made in that year.

A more accurate figure for the distribution of stillbirths, deaths and surviving infants may be obtained from the births in this hospital. In the five years prior to January 1, 1948, 99 infants with erythroblastosis were delivered. Twenty-four were stillborn, 29 died and 46 survived. Three of those who were born alive were extremely hydropic and never breathed. If these are omitted the mortality for 72 live born infants was 36%. The survival rate for all infants diagnosed as having erythroblastosis was 46%. About one-fourth of the total number were stillborn.

Pregnancies Following the Birth of the First Infant with Erythroblastosis

Ninety-six women have had one or more pregnancies following the birth of the first child on whom a diagnosis of erythroblastosis was made. Ten women have had only abortions, the majority of which are known to have been induced. The remaining 86 women have had a total of 147 children exclusive of abortions. Three of these infants were free of the disease; 144 were affected by erythroblastosis.

Among these 147 subsequently born children, 69 were stillborn, 63 died, 12 were affected but survived, and three were unaffected. One of the normal infants was Rh-negative as a result of artificial insemination. The other two were spontaneously Rh-negative. Of the 12 who were affected but who survived, three are known to have permanent brain damage.

The total number of erythroblastotic infants delivered in all pregnancies is 322. The number of affected children per mother exclusive of abortions is shown in Table III. Approximately half of the mothers have not had a pregnancy following the birth of a child with erythroblastosis. About 30% have had two pregnancies, 10% have had three and about 10% have had four or five. One woman has lost eight children, all presumably from erythroblastosis.

In this series the number of women who have given birth to an infant who has survived after once having given birth to an infant with erythroblastosis is very small. The remarkably small number of Rh-negative children born in subsequent pregnancies corroborates the supposition of Race and others that erythroblastosis is in some way related to the homozygosity of the father for Rh.

The survival of only 12 Rh-positive erythroblastotic infants who were born after the diagnosis had been made in an older sibling gives a very poor prognosis for subsequent childbearing if the diagnosis has once been established. The surviving Rh-positive and Rh-negative infants make up only 10% of the 147 who were delivered in subsequent pregnancies.

Abortions were not included in these figures because of the impossibility of knowing the number that were spontaneous. Twenty-six women had 32 abortions. In 12 women 13 are known to have been induced and it is probable that many of the others were also induced. Excluding the 13 known to have been intentional and adding the remaining 19 to the 147 pregnancies that went beyond the stage of abortion a total of 166 pregnancies is obtained. Eleven percent of these ended in abortion. This figure is similar to the percentage of abortions obtained in the control series of patients mentioned before. It seems reasonable to conclude, therefore, that pregnancies in Rh-negative immunized

women do not terminate more frequently in abortion than do those of non-immunized women.

Total Number of Erythroblastotic Infants

The addition of the 178 infants delivered as the first child known to have erythroblastosis to the 144 delivered in subsequent pregnancies makes a total of 322 erythroblastotic infants and fetuses. The number of affected infants delivered by each mother is shown in Table III. Approximately half of the mothers have had only one infant; the remainder have had from two to four with one patient having had eight.

The 322 infants are divided into 74 who lived, 123 who died and 125 who were stillborn. Of the infants who lived, all but 12 (16%) were the first affected child to be delivered. One hundred and thirty-two (53%) of the infants who died or were stillborn were delivered following the birth of an infant with erythroblastosis.

I have been fortunate in having had an opportunity to follow clinically 60 of the infants who survived and to perform postmortem examinations on 110 of this series who died or were stillborn.

Sex of Erythroblastotic Infants

It had been suggested in an earlier publication that more male than female infants were affected by erythroblastosis. The 322 erythroblastotic infants in the present study include 158 males, 132 females and 32 of unknown sex. Although the males are in slight preponderance the difference is not significant. Of the affected males 44 (28%) lived, 63 (40%) died and 51 (32%) were stillborn. Of the affected females 30 (23%) lived, 49 (37%) died and 53 (40%) were stillborn. The proportionate number of males who survived is slightly greater than the number of females but these figures are also not significant.

Infants Delivered at the Chicago Lying-in Hospital

The figures in the foregoing pages show the general outcome of a large group of women who have been immunized to the Rh factor and who have given birth to one or more infants with erythroblastosis. They include the women who have been delivered at the Chicago Lying-in Hospital but by separating these women from the others and discussing them as an individual group, information can be obtained that is not available in the larger series. This is especially true for the incidence of erythroblastosis in relation to maternal gravidity and total deliveries and for the proportionate numbers who were stillborn, died and survived.

Between January 1, 1935 and January 1, 1948, 111 women have given birth to 131 infants and fetuses with erythroblastosis at the Chicago Lying-in Hospital. Thirty-seven were stillborn, 45 died in the neonatal period and 49 survived.

Among the 82 who died or were stillborn, 41 (50%) had an older sibling affected with the same disease. Eleven more followed a pregnancy which terminated in abortion and eight followed a transfusion given after an abortion or following the birth of a normal infant. In only 22 (27%) was the preceding pregnancy not complicated by erythroblastosis, abortion or transfusion.

Among the 49 who lived only five (10%) had an older sibling with erythroblastosis. Two were born to a mother following transfusion unassociated with pregnancy, five followed a transfusion given after the birth of a normal child, and one followed an abortion.

This leaves 36 (73%) whose births were preceded only by normal pregnancies and without transfusions, and one whose mother gave no history of an earlier pregnancy.

The 58 affected infants whose birth had not been immediately preceded by an abortion, transfusion or erythroblastosis had a mortality rate of 38%; the 27 affected infants whose birth was immediately preceded by an abortion or transfusion had a mortality rate of 74%, a figure almost twice that for the first group; the 46 infants whose birth was preceded by the birth of an infant with erythroblastosis had a mortality rate of 90% (23 deaths, 18 stillbirths and five survivals).

Among the 94 infants who were born alive, the mortality rate for those whose birth had been preceded by that of an infant with erythroblastosis, a transfusion, or abortion was 72% (33 of 46); while for those whose birth followed that of a normal infant it was only 25% (12 of 48). The mortality rate for the entire group was 47%.

During the last five years the diagnosis has been made more frequently than it was in the earlier years. From January 1, 1935 to January 1, 1943 the number included three who survived, 16 who died and 13 who were stillborn. From January 1, 1943 to January 1, 1948 it included 46 who lived, 29 who died and 24 who were stillborn. This increase is partly artificial owing to the registration of some patients because of known Rh immunization. The greater frequency with which the diagnosis has been made on surviving infants is in some measure due to improved methods of diagnosis and more widespread recognition of the disease. This is not true of those who died or were stillborn for the criteria for the postmortem diagnosis of erythroblastosis have remained almost constant since 1935. There seems to have been an unexplained actual increase in the frequency with which the disease has been observd.

During the last five years 18,468 infants have been delivered in this hospital. Rh determinations on over 10,000 of the mothers showed approximately 14% to be Rh-negative. If the proportion were the same for the entire group, 2590 would have been Rh-negative. The gravidity of over 10,000 of the women is known and calculating the percentages to be the same for the entire group, the number of Rh-negative women of each gravidity is shown in Table IV.

The diagnosis was made during the last five year period on only three first born infants. The mother of two had been previously transfused so that only once did the disease appear among 1183 first born children of Rh-negative mothers who had not been given transfusions prior to pregnancy. All three of these infants survived.

The first affected child was born as a result of a second pregnancy in over one-third of the cases, and as a result of the third pregnancy in almost as many. The incidence of the disease increased from 1:24 among Rh-negative women in a second pregnancy to 1:6 among those in a fifth pregnancy (Table IV).

In this five year series the total incidence of erythroblastosis was one in 180 births and among Rh-negative women it was one in 26. Among Rh-negative primigravidas the incidence was one in 394. Among Rh-negative multigravidas the incidence was 1 in 15.

The following figures summarize the outcome of pregnancy in Rh-negative multigravidous patients:

6.7% delivered an infant with erythroblastosis.

4.0%, whose last preceding pregnancy ended in the birth of a normal child, delivered an infant with erythroblastosis.

2.5%, whose last preceding pregnancy ended in the birth of a normal child, had an erythroblastotic infant who survived.

1.5%, whose last preceding pregnancy ended in the birth of a normal child, had an erythroblastotic infant who died.

Antibodies in Relation to Outcome of Pregnancy

Davidsohn[1] has reported on the outcome of pregnancy in relation to the variety of Rh antibodies in 182 women. Most of the women giving birth to infants with erythroblastosis at the Chicago Lying-in Hospital were included in his study. He found that among 79 women whose infants survived, slightly more than twice as many (69.6%) had antibodies demonstrable both in saline and serum or albumin as in serum or albumin alone (30.4%). A figure not very different was found for mothers of infants who died after birth; 75.5% had both varieties of antibodies, 24.5% had antibodies demonstrable only in serum or albumin. Among the women giving birth to hydropic or stillborn infants saline and serum-albumin antibodies could be demonstrated in 31.5% while in 68.5% only serum-albumin antibodies could be found.

TABLE IV

Frequency with Which Erythroblastosis First Appeared in Offspring in Relation to Gravidity of Mother. The Chicago Lying-in Hospital January 1, 1943 to January 1, 1948

Gravidity of mothers	Total number of births	Number of births in Rh-negative women	Number of mothers of erythroblastotic infants	Incidence of mothers of erythroblastotic infants	
				Total women	Rh-negative women
Total	18,468	2,585	91	1:202	1:28
1	8,441	1,183	3	1:2814	1:394
2	6,020	843	35	1:172	1:24
3	2,345	328	29	1:81	1:11
4	997	139	15	1:66	1:9
5	259	36	6	1:45	1:6
6	166	23	3	1:55	1:8
over 6	240	33	0	0	0

The 73 women without saline antibodies had 37 (50%) fetuses who were stillborn or hydropic while the 109 women with both saline and serum-albumin antibodies had 17 (15%) who were stillborn or hydropic. The women without saline antibodies lost an additional 12 infants (16%) during the neonatal period while those with both varieties lost 37 (34%) after birth. The total mortality of the product of pregnancy for women with only serum-albumin antibodies was 49 (67%) while that for women with both varieties was 54 (50%).

It would seem from these data that when saline antibodies could be demonstrated, an affected fetus was somewhat less likely to be hydropic or stillborn than when only serum-albumin antibodies were present. A greater number of children who were born alive died subsequently when saline antibodies were present than when only serum-albumin antibodies could be demonstrated. The total survival rate (50%) was only 17% higher for the offspring of women with both varieties of antibodies than for those of women

with only serum-albumin antibodies (33%). The differences are not striking and from this material the demonstration of different varieties of antibodies seems to contribute relatively little of value toward a prognosis as to the eventual fate of the child in any given pregnancy.

It has been stated that the antibody which can be demonstrated by the use of cells suspended in saline is the first variety to be formed and that an antibody which can be demonstrated only by the use of cells suspended in serum or albumin is a later variety to appear. The latter is consequently thought to be evidence of more severe immunization. Consequently, the presence of the saline type of antibody alone would be expected to be associated with a somewhat lower mortality than an antibody that can be demonstrated only in serum or albumin. Although this holds generally true for a large series the outcome in a single case cannot be foretold with any degree of certainty from the variety of antibody that is found in the maternal blood.

Discussion

One of the most striking observations in the foregoing data is the difference in mortality rates among the infants who are the first on whom a diagnosis of erythroblastosis is made and among those having an older sibling with erythroblastosis. This difference is particularly noticeable when the last pregnancy preceding the birth of the eldest child with erythroblastosis has not resulted in an abortion or been complicated by a transfusion. In such instances the combined fetal and neonatal mortality is 61% in comparison to 92% for those infants with older affected siblings.

Since 1941 almost all infants with erythroblastosis who have been transfused in this hospital have been given Rh-negative blood. At different times it has been the practice to use whole blood in small transfusions, whole blood in exchange transfusions, concentrated cells with most of the plasma removed and cells washed free of plasma. No appreciable difference in mortality rates has been observed in relation to any specific variety of treatment.

Antibody studies have contributed very little toward the ability to prognosticate the fate of the infant. We believe that under no circumstances is it justifiable to conclude, on the basis of any laboratory data, that a certain chain of events will follow; as, for instance, that a stillbirth would be inevitable if early delivery were not undertaken.

It seems quite certain that many infants who die or are stillborn without a diagnosis of erythroblastosis having been made on an older surviving sibling are not in reality the first affected child to be born to that mother. Many infants are being recognized at present as suffering from the disease who a few years ago would have passed as normal because blood studies were not made and because their symptoms were mild and self-limited.

The data presented seem to justify the following conclusions:

1. When immunization occurs during the course of a pregnancy the effect on the fetus carried during that pregnancy is minimal and the child ordinarily has few or no symptoms and survives. This accounts for the infrequency with which the disease appears in first pregnancies and for the failure of the child to be affected even though antibodies are found in the maternal blood late in a pregnancy.

2. When immunization has been initiated or enhanced prior to the current pregnancy by transfusions, abortions or by any complication of pregnancy that has facilitated the

entrance of fetal blood cells into the maternal circulation, the effect on the fetus is greater and the chance of survival is lessened.

3. When a sufficient degree of immunization has been established to produce the disease in one infant, the effect in a subsequent conception is much more dramatic and the chance of survival of that infant is very poor.

Because of these facts it becomes evident that the obstetric history of the mother and the condition of the older siblings must be taken into account in attempting to evaluate any method of therapy in relation to the fate of a particular infant or group of infants. Saving the lives of a dozen children whose mothers have previously given birth to infants with erythroblastosis is an entirely different matter from saving the lives of an equivalent number of children who have had no older siblings with the disease. Even though some of the latter group are severely affected their outlook is better than is the outlook of those of apparently equal severity who belong in the first group.

Since the outlook for the outcome of subsequent pregnancies is so intimately associated with the diagnosis in the current pregnancy it cannot be reiterated too frequently that every attempt should be made to establish a correct diagnosis in each case. The death of one child of an Rh-negative woman does not mean the same fate for all her children. An Rh-negative woman can lose a child from the same causes responsible for death in the children of Rh-positive women and in no case is the single fact that a woman is Rh-negative and her husband Rh-positive enough to make a statement that Rh incompatibility is responsible for death.

There has been much discussion concerning the relation of Rh immunization to abortions. No evidence has been forthcoming as a result of our own studies or those of other investigators to show that repeated abortions in women who have never carried a fetus to viability—the so-called "habitual abortions"—have any relation to Rh-immunization. The majority of such women have been shown to be Rh-positive. A few have been Rh-negative but without evidence of immunization.

It must be remembered, however, than an Rh-negative patient may become immunized during the course of any abortion; five patients in our series had no pregnancies except those terminating in abortion preceding the birth of an infant with erythroblastosis.

As stated earlier, the incidence of abortion following the birth of an infant with erythroblastosis is no greater than the incidence of abortion in normal non-immunized women. There seems no reason to believe that immunization is responsible for abortions; there is evidence, on the other hand, to indicate that abortions may be associated with the development of the immune state.

During 1946 and 1947, 44 infants and fetuses on whom a diagnosis of erythroblastosis was made were delivered at the Chicago Lying-in Hospital. Of these 10 were stillborn, 10 died after birth and 24 survived. *In no instance did a live born infant die whose birth had not been preceded by that of an infant with erythroblastosis. In only two instances did an infant survive whose birth had been preceded by that of an infant with this disease.*

Summary

One hundred and seventy-five women observed since 1934 who became immunized to Rh at some time during their reproductive careers had a total of 699 pregnancies prior to January 1, 1948. They had 341 pregnancies preceding the birth of the first infant with

erythroblastosis. These resulted in seven stillbirths, 13 neonatal deaths, 65 abortions and 256 surviving children. Forty-four of these abortions followed the birth of the last normal child and preceded the birth of the first child with erythroblastosis. The average number of surviving children born to each patient before the birth of an infant with erythroblastosis was 1.4.

The diagnosis of erythroblastosis was made for the first time in seven women in a first pregnancy and 168 women in second or subsequent pregnancies. Four of the women without earlier pregnancies had had transfusions. Of the 178 affected infants 56 died before birth, 60 died after birth and 62 survived.

Ninety-six women had 179 pregnancies following the birth of an infant with erythroblastosis. These have ended in the birth of 3 Rh-negative, 144 Rh-positive infants with erythroblastosis and 32 abortions. Thirteen of the abortions are known to have been induced. Sixty-nine of the Rh-positive infants were stillborn, 63 died and only 12 survived. Three of the latter are known to have brain damage.

The 322 infants with erythroblastosis included 158 males, 132 females and 32 of unknown sex. Twenty-eight percent of affected males and 23% of affected females survived.

Among 131 infants with erythroblastosis delivered in the Chicago Lying-in Hospital the mortality rates were: 38% for 58 infants whose birth had not been immediately preceded by a transfusion, abortion or erythroblastosis in a sibling; 74% for 27 infants whose birth was immediately preceded by an abortion or a transfusion; 90% for 46 infants whose birth was preceded by that of an infant with erythroblastosis.

Among 18,468 deliveries at the Chicago Lying-in Hospital in the last five years the frequency with which erythroblastosis occurred for the first time varied from once in 2,814 deliveries for women in their first pregnancies to 1:172 in second pregnancies and in 1:55 for sixth pregnancies.

In the last two years no live born infant has died of erythroblastosis in this hospital who has not had an older sibling affected by the same disease.

In evaluating any method of treatment the previous reproductive histories of the mothers of the treated infants must be taken into account. In our hands the previous maternal history has been of more value in prognosticating the fate of an infant born to an immunized Rh-negative woman than have changes in maternal antibody titer or differences in the variety of antibodies present.

Reference

1. Davidsohn, I., Stern, K., Interpretation of Rh anti-bodies, Am. J. Clin. Path. In press.

Spanish Abstract

Casos Reproductivos de Madres de 322 Infantes con Eritroblastosis

Las 175 mujeres bajo observación de 1934 a 1947, quienes se volvieron inmunes al Rh, tuvieron un total de 699 embarazos: 341 precedente al nacimiento del primer niño con eritroblastosis, habiendo resultado siete partos muertos, 13 muertes neonatales, 65 abortos y 256 niños vivos. De los abortos 44 siguieron el nacimiento del último niño normal y precedieron el del primer niño con eritroblastosis. El promedio de los niños nacidos, que le quedaron vivos, a cada paciente antes del nacimiento de un infante con eritroblastosis fué 1.4.

La diagnosis de la eritroblastosis se hizo por la primera vez a siete mujeres en el primer embarazo y a 168 en el segundo o subsecuentes embarazos. Cuatro de las mujeres que no habían tenido em-

barazos anteriormente habían recibido transfusiones. De los 178 infantes afectados 56 murieron antes del parto, 60 murieron después del parto y 62 vivieron.

Noventa y seis mujeres tuvieron 179 embarazos después del parto de un niño con eritroblastosis, resultando en el nacimiento de tres infantes Rh-negativos (normales), 144 infantes Rh-positivos con eritroblastosis y 32 abortos, 13 de los cuales se sabe fueron inducidos. De los infantes Rh-positivos 69 fueron partos muertos, 63 murieron y 12 vivieron, tres de los cuales tenían estropeo en el cerebro.

Los 322 infantes con eritroblastosis incluyeron 158 varones, 132 hembras y 32 de sexo desconocido. Los que vivieron fueron 28% de los varones y 23% de las hembras.

Entre los 131 infantes con eritroblastosis que nacieron aquí, la mortalidad fué 38% de los 58 infantes cuyo parto no había sido inmediatamente precedido de una transfusión, aborto o eritroblastosis; 74% de los 26 infantes cuyo parto fué inmediatamente precedido por aborto o transfusión; 90% de los 46 infantes cuyo parto fué precedido por el de un niño con eritroblastosis.

Entre 18,468 partos aquí en los últimos cinco años, la frecuencia con que la eritroblastosis ocurrió por la primera vez varió de 1:2,814 en los primeros embarazos a 1:172 en los segundos embarazos y en 1:55 en los sextos embarazos. En los últimos dos años ningún infante nacido vivo ha muerto de eritroblastosis aquí que no haya tenido un niño mayor afectado.

Al avaluar cualquier tratamiento, hay que considerar los casos reproductivos maternos de los infantes. Aquí el caso anterior materno ha resultado de más valor al pronosticar el destino de un niño nacido de una mujer Rh-negativa inmunizada que los cambios en el título anticuerpo o diferencias en la variedad de anticuerpos presentes.

5841 *Maryland Ave.*

GROWTH OF THE HEART RELATED TO BODILY GROWTH DURING CHILDHOOD AND ADOLESCENCE

By MARION M. MARESH, M.D.
Denver, Colo.

ALTHOUGH it is a relatively simple procedure to measure the heart as seen in roentgenograms of the chest, evaluation of its actual size is much less accurate than are the methods of measurement. No one standard of "normal" values or range of variation has yielded any precise separation of the normal from abnormal sized hearts. A heart that is near the upper limits of so-called normal variation in size may in one instance be a healthy heart for a child who has always had a relatively large heart, and in another instance be the pathologically enlarged heart of a child who, in earlier childhood, had a smaller heart than is usually seen. It frequently happens that the cardiologist, radiologist, and the pediatrician are presented with the problem of judging the size of the heart without knowledge of how that heart appeared when the child was well. One of the satisfactions of a longitudinal study such as is being carried on at the Child Research Council is that one can go back to earlier data, when a health problem arises, and weigh the present status against the past. This report on the size of the heart from childhood through adolescence was undertaken to discover if such a longitudinal approach might enable one to limit the range of variation for an individual child. It seemed possible that the increase in size of the heart might bear a discernible relation to the general pattern of growth. A further question to be answered was whether body build during childhood was a determining factor in either the size or shape of the heart.

MATERIAL FOR STUDY

At the Child Research Council, a group of healthy children have been studied during the past 20 years. As part of that study, roentgenograms of the chest have been taken at frequent intervals from birth to the present time. Only those films taken in the erect, postero-anterior position and at a seven foot focal-film distance were included in these data. This eliminated from the series all films on children younger than four years of age since we take roentgenograms of the chest on those children from the supine position with a shorter focal-film distance. Technic has always been kept as constant as possible; milliamperage has been 100-125, exposure time has been 1/20 second and KVP has varied with the age of the child from 75 to 105.

The roentgenograms measured included all the chest films taken from the erect position on 71 boys and 57 girls who have been under study at the Child Research Council. The number of films for each person varied with their present age and ranged from less than 10 for some of the younger children to over 40 for those who are now adults. A total of 3205 roentgenograms were measured. Well over half the subjects are now post-pubescent. Since most of the roentgenograms were taken at routine visits to the Child Research Council, body height and weight were also recorded. Visits were usually made at regular intervals—four times a year during the earlier years of the

From the Child Research Council and the University of Colorado School of Medicine.

This investigation was supported (in part) by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

(Received for publication May 9, 1948.)

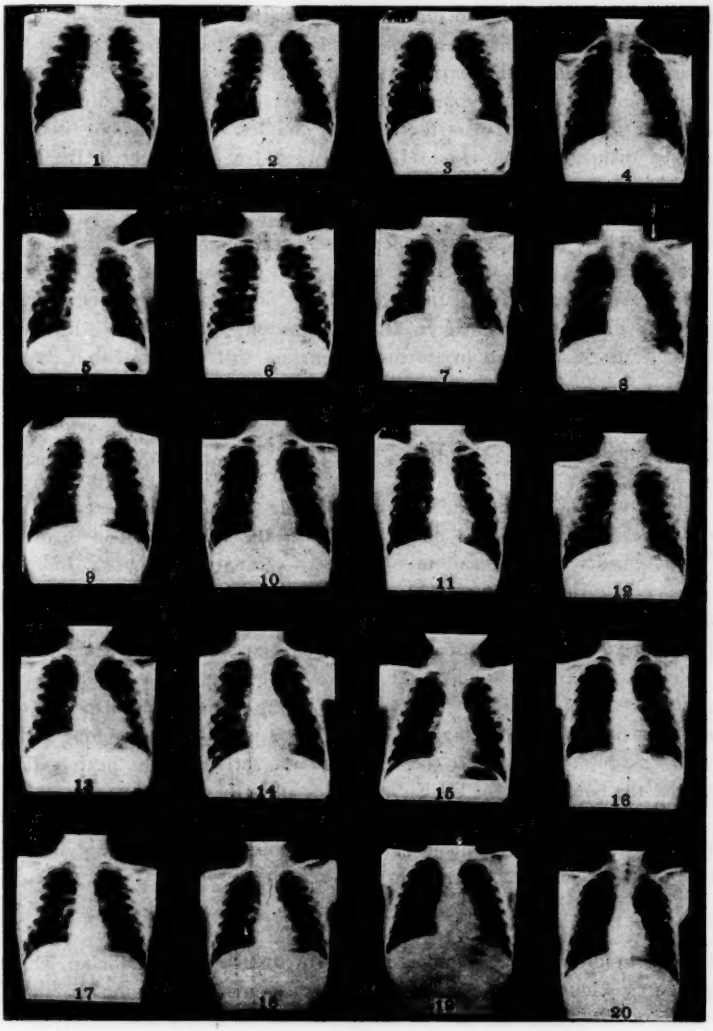


FIG. 1. Reproductions of roentgenograms of the chest at eight years of age of 20 boys who are under study at the Child Research Council.

institution and semi-annually or annually in recent years because of the scarcity of X-ray film and because we found that there was less need for frequent roentgenograms of the chest as the child matured.

The measurements made from the roentgenograms were: (1) transverse diameter of the heart (TD), the sum of the greatest horizontal distance from the midline of the thorax to the right cardiac margin and the greatest distance from the midline to the left cardiac margin; (2) long diameter of the heart (LD) which extends from the junction of the cardiac and vascular silhouette on the upper part of the right border of

the heart obliquely downward to the apex on the left side; (3) broad diameter of the heart (BD), the greatest diameter perpendicular to the long diameter extending from the upper limit of the left ventricular contour, as near as it can be judged, to the lowermost point of the right border of the heart or as it is usually measured, the summation of the perpendiculars to the right and left from the long diameter; and (4) internal diameter of the chest (ID) measured from the right to the left pleural surfaces through the dome of the right side of the diaphragm and parallel to the transverse diameter. All measurements were made by one person (M.M.). Each film was remeasured at a later time to give an independent check on the first set of values. The two sets of measurements were averaged if they agreed within 1 mm. for TD and ID. If not, further measurements were made till check values were obtained. LD and BD measurements did not always agree as closely as one would have wished, probably because they are less precise measurements. Values that agreed within 3 mm. were accepted as within the limits of error and these were also averaged to give the figures listed in Tables VII and VIII. Sample measurements for eight children, along with age, height, weight, and the calculated cardio-thoracic ratio ($\frac{TD}{ID}$) are appended as Tables VII and VIII. The complete data on the 128 subjects are available upon request from the author. No statistical work was done with either the long or broad diameters since these measurements were difficult to obtain with certainty or accuracy and since they showed essentially the same pattern of fluctuations as did transverse diameter measurements. Because there is so much variation in the shape of different hearts, it would be desirable to have another measurement of cardiac size that could be obtained with as much reliability as transverse diameter. However, it did not seem that breadth and length measurements aided materially in visualizing the cardiac shape. Cardiac area measurements have also been suggested for greater precision in defining cardiac size. If it were possible to reconstruct the diaphragmatic surface of the heart with accuracy and to limit the borders of the cardiac chambers at the base, cardiac area measurements might be more useful. Practically, we have found that area measurements show much the same variation as do the diameter measurements and seem to add little to one's estimate of size by less time-consuming methods.

Results

Variations in cardiac shape and size are very common in childhood. The "typical average heart" seldom obtains on routine roentgenograms. Variations in the size and prominence of the pulmonary artery contours, in the curvature and length of the right border, in the width and curvature of the lower left border, as well as variations in the angulation of the long axis all serve to produce hearts of such different shapes that it is difficult to think of any one shape as the "normal." Examples are shown in Fig. 1 and 2 of roentgenograms of the chest of 20 boys and 20 girls at eight years of age. The variations in size are obvious. The variations in shape include some that we have been trained to think of as consistent with cardiac disease or congenital malformations. However, these are healthy children according to our present estimates of health. It seems more likely that we should revise our estimate of what constitutes a "normal" cardiac shape than that we should consider a high percentage of these hearts as abnormal on the basis of cardiac shape. The boy's chest shown in Fig. 1-19, for example, shows a cardiac shape that would be difficult to accept as a healthy one if it were not that the

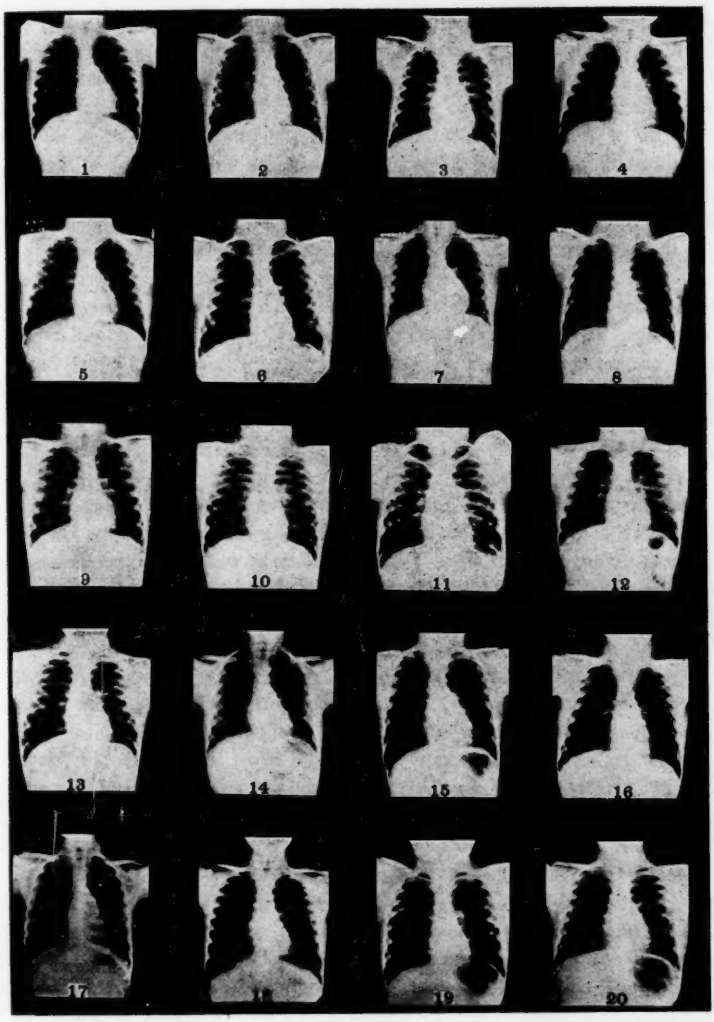


FIG. 2. Reproductions of roentgenograms of the chest at eight years of age of 20 girls who are under study at the Child Research Council.

physical and functional examinations since infancy have never shown any abnormal findings. Another boy, Fig. 1-15, has been thought clinically to have a minor congenital cardiac defect on the basis of the electracardiographic findings and the persistence of a fairly rough systolic murmur although he has never had any impairment of health or functional ability. His cardiac shape and size are not unusual in any respect. The chest films of the girls shown in Fig. 2 show less extreme variations in shape but the relations between cardiac size and body size show poor correlation on first inspection. The smallest heart, Fig. 2-2, and the largest heart, Fig. 2-11, in this group are seen in

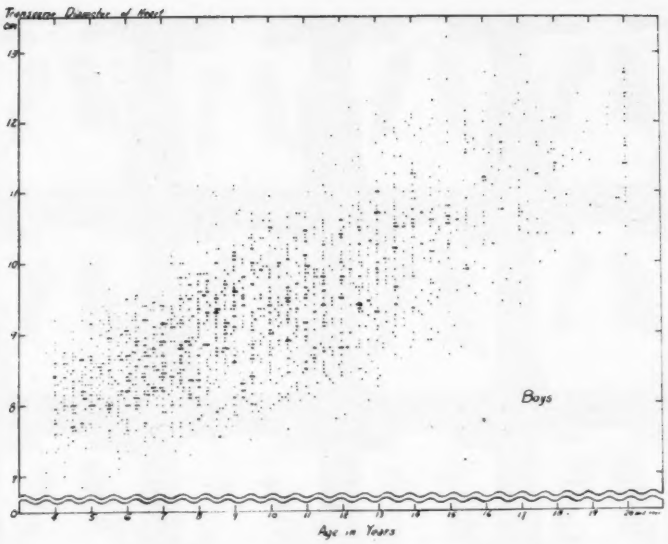


FIG. 3. Scatter chart of measurements of transverse diameter of heart graphed against chronologic age. Transverse diameter measurements were made from 1,834 roentgenograms of the chest of 71 boys under study at the Child Research Council.

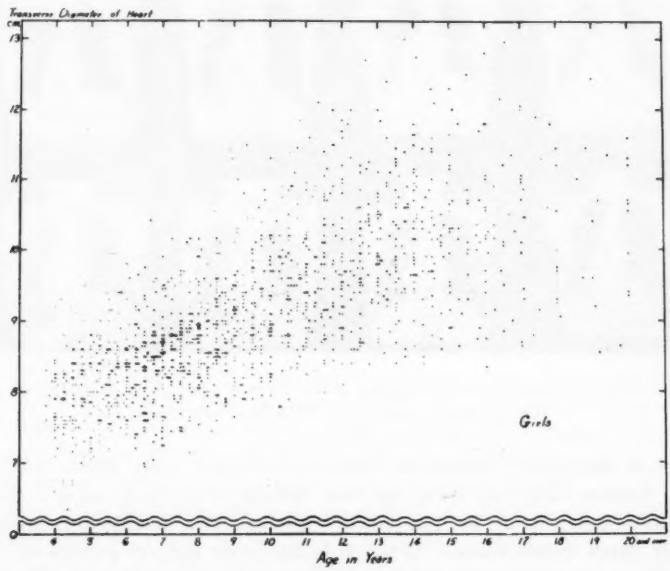


FIG. 4. Scatter chart of measurements of transverse diameter of heart graphed against chronologic age. Transverse diameter measurements were made from 1,371 roentgenograms of the chest of 57 girls under study at the Child Research Council.

girls well above average height and weight for their age. The smallest of these girls, Fig. 2-1, has a cardiac shadow of only slightly less than average size while the largest girl, Fig. 2-6, has a heart of almost exactly average size.

It would seem, from looking at a series of hearts of such different shapes and sizes as these, that knowing the average values for cardiac measurements at eight years of age would be of limited value in estimating expected size and would contribute very little to the description of cardiac shape. The range of variation in transverse diameter is quite great, as shown in Fig. 3 and 4, where transverse diameter of the heart is graphed against age. An increase in size with advancing age is also obvious, in spite of this wide range. Mean values for transverse diameter of the heart were therefore calculated and are given in Table I. These mean values show an orderly increase through childhood and adolescence as well as a significant sex difference. The girls, with lower mean values from four through eight years, show a rise above the mean values for boys from nine through 12 years. From 12 years on the boys again have larger average values for cardiac transverse diameter than girls. This same sex difference is seen in the mean weight and height values for each age level, as also seen in Table I, and is in agreement with the well known occurrence of earlier adolescent growth spurts for girls.

Since the mean values for transverse diameter of the heart, internal diameter of the chest, height, and weight all increased in much the same manner from childhood through adolescence, it seemed advisable to inspect the curves of each individual for a possible relationship between the general pattern of bodily growth and increase in size of the heart and chest. The heart measurements were found to show a great deal of fluctuation from film to film. Some of that fluctuation may be due to the different phases of the cardiac cycle during which the roentgenograms were taken. For cardiac size alone, it would be desirable to take roentgenograms of children with at least one second exposure so as to obtain a silhouette which is not influenced by the phases of the cardiac cycle. However, such exposures produce unsatisfactory roentgenograms of the lung fields and are not useful for routine examinations of the chest. The degree of inspiration may also have affected the measurements somewhat but only those films that were deemed satisfactory from a technical standpoint were measured. Some of the fluctuations seem unusually great; but, on the whole, a pattern of increase in size of the heart is apparent regardless of the irregularities of the curves. Representative samples of these curves are shown in Fig. 5 and 6 along with mean values and the range included in plus or minus one standard deviation from the mean for height, weight, internal diameter of the chest, and transverse diameter of the heart. The data for these graphs are given in Tables VII and VIII. In the majority of cases there is good agreement between the pattern of bodily growth as reflected in the curves for height, weight, and internal diameter of the chest and the pattern of cardiac growth as seen in the curves of the cardiac diameters. The increase in cardiac size near the peak of the adolescent growth spurt is seen too consistently to be discounted as being due to chance variations in measurements. It would seem much more likely that the sudden acceleration of bodily growth that is associated with puberty is accompanied by an actual increase in size of the heart, perhaps due to greater demands being put upon it during this period. Increases in cardiac size during adolescence should probably therefore be interpreted in terms of the strength of the growth spurt. Granting that the cardiac measurements do not graph out as smooth curves, most individuals show a pattern of increase in cardiac measurements that does not differ materially from the pattern of

TABLE I

RESULTS OF MEAN AND STANDARD DEVIATION CALCULATIONS* ON 3205 ROENTGENOGRAPHIC EXAMINATIONS OF 71 BOYS AND 57 GIRLS UNDER STUDY AT THE CHILD RESEARCH COUNCIL

Age	Number		T.D.: Mean and S.D. (cm.)		I.D.: Mean and S.D. (cm.)		Height: Mean and S.D. (cm.)		Weight: Mean and S.D. (kg.)	
(yr.)	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
4	130	112	8.22±.46	7.94± .50	18.79± .74	18.14± .84	106.99±3.40	106.61±4.50	17.65±1.40	17.32±1.87
5	168	126	8.40±.56	8.14± .57	19.48± .80	18.79± .96	113.87±3.89	113.95±4.75	19.95±1.74	19.62±2.26
6	175	145	8.60±.53	8.34± .57	20.11± .90	19.40± .96	120.68±4.20	120.55±5.36	22.21±2.05	21.81±2.77
7	164	146	8.82±.64	8.58± .62	20.85± .93	20.05±1.07	127.28±4.39	126.52±5.96	25.18±2.46	24.77±3.67
8	169	136	8.97±.70	8.84± .63	21.45±1.04	20.72±1.17	132.69±4.66	132.66±5.76	28.08±3.09	27.93±4.48
9	164	118	9.17±.79	9.16± .74	22.08±1.17	21.59±1.22	137.79±4.74	138.62±6.32	30.80±3.75	31.79±5.69
10	151	104	9.28±.70	9.41± .84	22.49±1.25	22.36±1.36	142.42±4.90	144.14±7.20	33.49±4.10	35.62±6.64
11	142	100	9.55±.77	9.71± .87	23.11±1.33	23.09±1.47	146.73±5.42	150.32±7.65	36.20±4.75	39.56±8.23
12	135	93	9.80±.83	9.87± .93	23.86±1.39	23.87±1.63	151.96±5.67	156.44±7.50	40.01±5.74	43.98±9.16
13	123	92	10.13±.89	10.07± .89	24.81±1.72	24.61±1.63	158.04±6.54	161.70±6.73	45.06±7.16	48.48±8.94
14	97	73	10.47±.87	10.24± .80	26.07±1.90	25.28±1.61	164.97±6.84	165.17±5.69	50.85±7.37	52.01±8.71
15	71	43	10.80±.85	10.29± .93	26.71±1.81	25.53±1.82	170.62±6.41	166.44±5.39	55.60±7.01	53.41±8.89
16	48	34	11.08±.82	10.34±1.09	27.31±1.95	25.65±1.69	175.25±5.11	167.34±5.35	60.31±6.99	54.68±8.70
17	39	21	11.18±.82	10.44±1.07	27.57±2.18	25.71±1.67	176.41±4.59	165 93±4.45	62.37±7.47	54.78±7.37
18 and over	58	28	11.57±.67	10.28±1.00	29.01±2.39	25.50±1.59	179.50±6.35	165.82±3.90	66.49±7.04	55.26±5.33

* Notes: N refers to number of T.D. measurements available. This occasionally varied by +1 or +2 from number of height and weight measurements available, and adjustments were made accordingly.

T.D.—Transverse diameter of heart measured from PA roentgenogram of chest.

I.D.—Internal diameter of chest measured from PA roentgenogram of chest.

Ht.—Standing height measured at time of roentgenographic examination.

Wt.—Weight measured at time of roentgenographic examination.

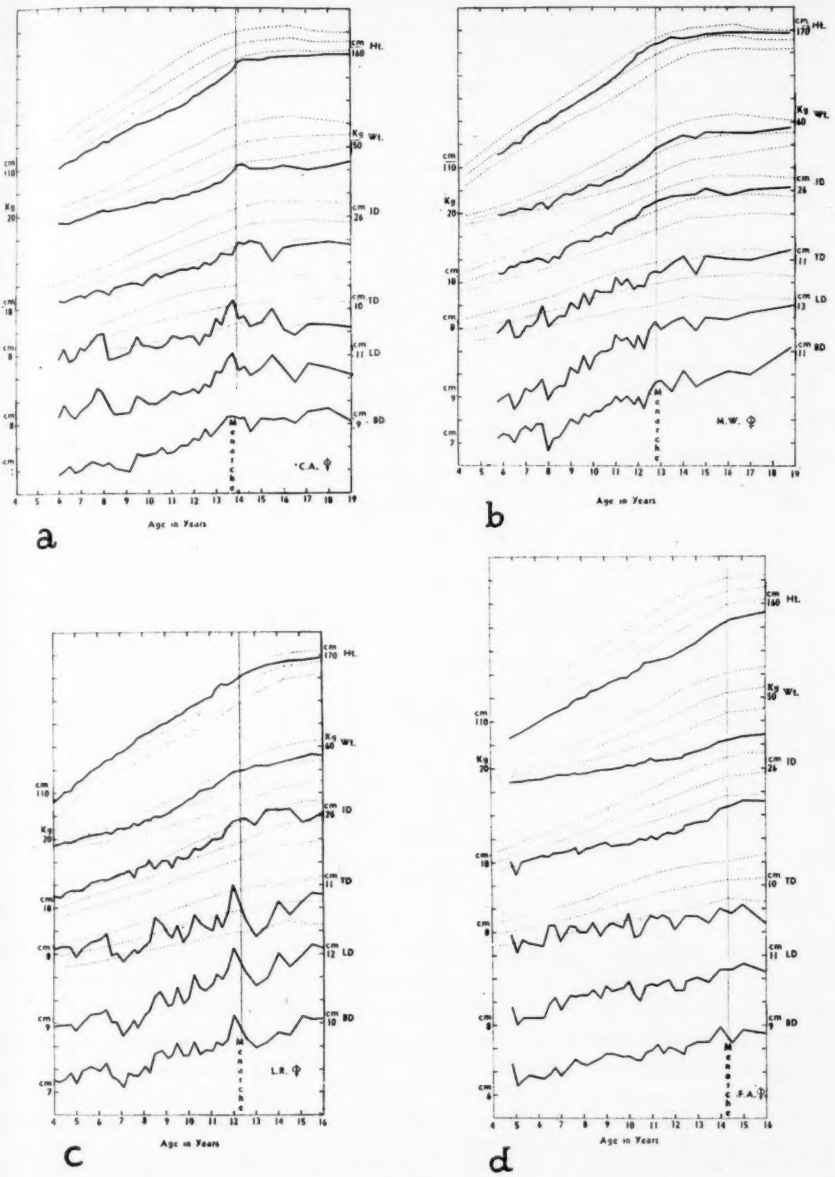


FIG. 5. Individual measurements of height; weight; internal diameter of chest; transverse diameter, long diameter, and broad diameter of heart for four girls representative of 57 girls under study at the Child Research Council; all measurements referred to age in years. Dotted lines represent mean values and zone included in plus and minus one S. D. from means calculated from original data.

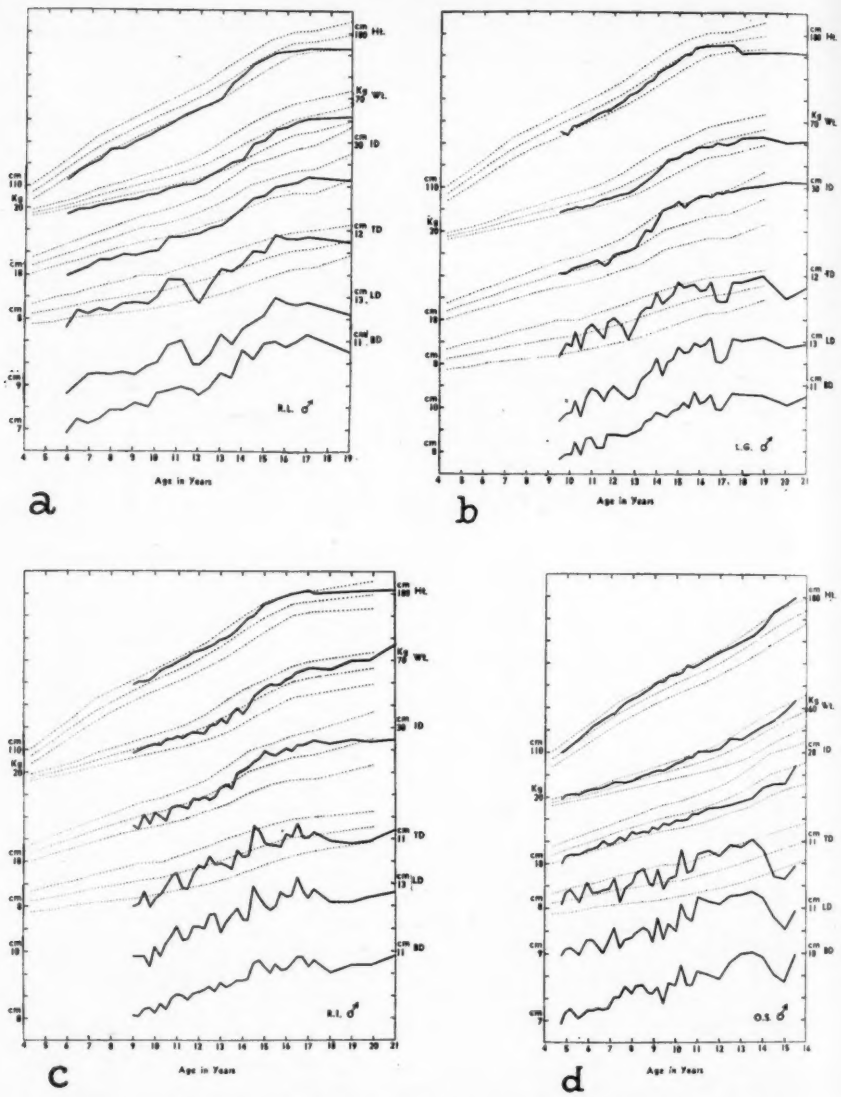


FIG. 6. Individual measurements of height; weight; internal diameter of chest; transverse diameter, long diameter, and broad diameter of heart for four boys representative of 71 boys under study at the Child Research Council; all measurements referred to age in years. Dotted lines represent mean values and zone included in plus and minus one S. D. from means calculated from original data.

bodily growth. The relative curves are not absolutely alike—that is, a child whose height and weight are average will not show cardiac measurements that are exactly average. But the curves do seem to bear a perceptible relation to each other both as to rate of acceleration and relative zones of variation within the group. In most girls a

TABLE II

COEFFICIENTS OF CORRELATION BETWEEN TRANSVERSE DIAMETER OF HEART AND MEASUREMENTS OF HEIGHT, WEIGHT AND INTERNAL DIAMETER OF CHEST. DATA FROM 3205 ROENTGENOGRAPHIC EXAMINATIONS OF 71 BOYS AND 57 GIRLS UNDER STUDY

Age	Number		Correlation of measurements of T.D. with I.D., height and weight					
			r: T.D./I.D. and S.D. of r		r: T.D./Ht. and S.D. of r		r: T.D./Wt. and S.D. of r	
(Yr.)	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
4	130	112	.37± .08	.45± .08	.26 ± .08	.48± .07	.40± .07	.58± .06
5	168	126	.42± .06	.54± .06	.32 ± .07	.35± .08	.47± .06	.47± .07
6	175	145	.46± .06	.44± .07	.31 ± .07	.29± .08	.48± .06	.44± .07
7	164	146	.39± .07	.50± .06	.13 ± .08	.32± .07	.30± .07	.43± .07
8	169	136	.40± .06	.54± .06	.09 ± .08	.28± .08	.31± .07	.43± .07
9	164	118	.48± .06	.60± .06	.11 ± .08	.31± .08	.39± .07	.61± .06
10	151	104	.48± .06	.67± .05	−.008± .08	.47± .08	.39± .07	.66± .06
11	142	100	.51± .06	.65± .06	.11 ± .08	.37± .09	.37± .07	.65± .06
12	135	93	.63± .05	.74± .05	.13 ± .09	.33± .09	.51± .06	.69± .05
13	123	92	.63± .06	.62± .07	.13 ± .09	.21± .10	.51± .07	.56± .07
14	97	73	.62± .07	.68± .07	.09 ± .10	.19± .11	.22± .10	.58± .08
15	71	43	.55± .09	.59± .10	−.05 ± .12	.09± .16	.39± .10	.58± .10
16	48	34	.49± .12	.81± .06	−.04 ± .15	.16± .17	.36± .13	.67± .09
17	39	21	.50± .13	.74± .10	.09 ± .16	.37± .20	.49± .12	.74± .10
18 and over	58	28	.49± .11	.60± .13	.34 ± .12	.24± .18	.51± .10	.58± .13

Notes: Number refers to T.D. measurements available. This varied occasionally by +1 or +2 from number of measurements available for I.D., Ht., and Wt. and adjustments were made accordingly.

T.D.—Transverse diameter of heart measured from PA roentgenogram of chest.

I.D.—Internal diameter of chest measured from PA roentgenograms of chest.

Ht.—Standing height measured at time of roentgenographic examination.

Wt.—Weight measured at time of roentgenographic examination.

r—Coefficient of correlation.

S.D. of r—Standard deviation of coefficient of correlation.

sharp increase in cardiac size is closely related to the menarche (Fig. 5-a and 5-c). In others, such as shown in Fig. 5-b, the increase in size is continued after the menarche along with further increase in weight. And in an occasional girl such as the one shown in Fig. 5-d there is no sharp adolescent growth spurt nor is there an appreciable change in the diameter measurements. In most boys the increase in the cardiac measurements follows the curve for increase in bodily size with the maximum increase during adolescence. A few children such as the boy illustrated in Fig. 6-d show a decrease or a lag in cardiac measurements at a time when one might reasonably have expected an increase according to the height and weight increments. It should be emphasized again that the curves for increase in the cardiac measurements do not follow with exactness the height or the weight curves. The similarities are great enough, however, to justify the concept of an increase in cardiac size synchronous with bodily growth in height, weight, and width of the chest. Thus while the range of variation in diameter measurements of the heart is great as seen in Fig. 3 and 4, and while the consecutive roentgenograms of any individual give measurements that fluctuate to some degree, it is still possible to

limit the range in cardiac diameter measurements for an individual and to compare the increase in those measurements with the increase in body size during childhood and adolescence.

One might reasonably expect, therefore, that a highly positive correlation coefficient could be calculated between the transverse diameter measurements of the hearts of all children and their height, weight, and internal diameter of the chest. These are given in Table II. All the correlations with height are very poor, ranging from −0.05 (no correlation at all) to +0.48. The correlation coefficients for transverse diameter with

TABLE III

MEAN VALUES FOR TRANSVERSE DIAMETER OF HEART FOR INDIVIDUALS SEPARATED INTO OVERWEIGHT, MEDIUM-WEIGHT OR UNDERWEIGHT GROUPS. MEASUREMENTS TAKEN FROM 3205 ROENTGENOGRAPHIC EXAMINATIONS ON 71 BOYS AND 57 GIRLS UNDER STUDY

Boys			*Age* (yr.)	*Girls*		
Overweight for height	Medium-wt. for height	Underweight for height		Overweight for height	Medium-wt. for height	Underweight for height
(cm.)	(cm.)	(cm.)		(cm.)	(cm.)	(cm.)
8.15	8.34	8.05	4	8.30	7.78	7.93
8.52	8.45	8.21	5	8.38	8.02	8.11
8.71	8.68	8.39	6	8.65	8.26	8.16
9.06	8.78	8.66	7	8.98	8.49	8.34
9.27	8.98	8.71	8	9.36	8.72	8.58
9.66	9.23	8.75	9	9.77	8.96	8.77
9.78	9.33	8.90	10	10.24	9.24	8.81
10.00	9.56	9.26	11	10.46	9.50	9.19
10.34	9.86	9.39	12	10.60	9.78	9.14
10.87	10.21	9.57	13	10.83	9.72	9.60
11.12	10.60	9.86	14	10.91	10.06	9.72
11.61	10.92	10.29	15	11.21	10.15	9.80
11.75	11.06	10.70	16	11.16	10.35	9.44
11.67	11.10	10.91	17	11.31	10.26	9.34
11.82	11.53	11.15	18 & over	11.23	10.19	9.03

weight and with internal diameter of the chest are somewhat better than with height but are not high and range from +0.22 to +0.81 at different age levels. Such coefficients of correlation would seem to be sufficiently low to make prediction of transverse diameter of limited value. They were most discouraging since it seemed probable that there was correlation between the various measurements from inspection of the individual curves. Statistically that correlation could not be proved, probably because of the amount of fluctuation of the cardiac measurements.

Since the graphs of transverse diameter of the heart for each individual did seem to be related to bodily growth, an attempt was made to find that relationship on some basis other than statistical calculations based on actual values of height and weight. The boys and girls were separated into three groups irrespective of their height levels. These were: (1) those who were over weight for their height (fat); (2) those whose height and weight were proportionate (medium); and (3) those who were under weight for their height (thin). Thus in each group there were tall children, short children, and children of average height. An occasional child changed his height-weight

relationship during childhood so that it was necessary to separate his data into two parts and classify each part individually. For instance, he might have been classified as thin up to 10 years of age and of medium build after that time. Some of the groups were small and the mean values do not form as smooth curves as when larger samples are available. These means for each group are shown in Table III and illustrated in Fig. 7. There is apparent a definite difference in the mean values for transverse diameter of the heart for the three groups of both boys and girls. The mean transverse cardiac

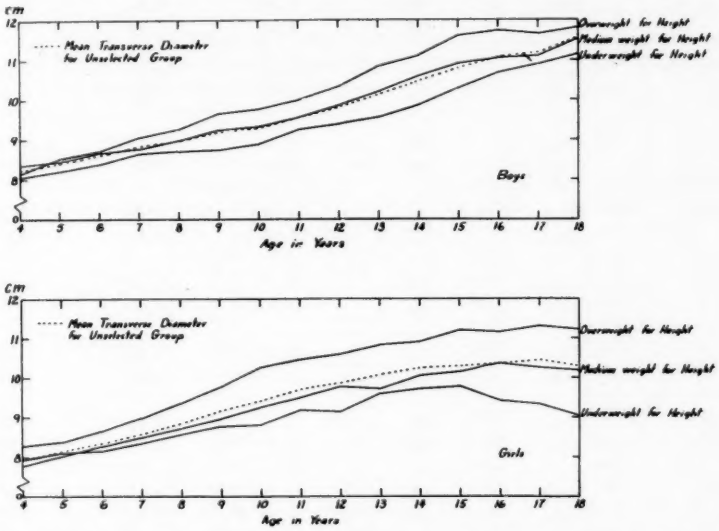


FIG. 7. Mean values for measurements of transverse diameter of heart graphed against chronologic age for overweight, medium-weight, and underweight groups of boys and girls under study at the Child Research Council. Mean transverse diameter of heart as calculated from unselected data is shown as a dotted line in each graph.

diameter after five years of age was greatest for Group I (fat), least for Group III (thin), with Group II intermediate and near the mean values for the entire group at each age as given in Table I. It would seem, therefore, that the height-weight relationship may well be a determining factor in the size of the heart during childhood, even though height itself is poorly correlated with cardiac measurements during this same period as shown by coefficients of correlation in Table II. This is illustrated in Fig. 6-c, a child who was thin for his height through 14 years of age and then changed to a boy of proportionate height and weight. Transverse diameter of the heart was below the mean through 14 years of age and then increased to equal or surpass the mean values during the adolescent period. It seems logical to suppose that the relatively greater weight during adolescence may have been partially responsible for the increase in size of the heart.

The use of cardio-thoracic ratios for evaluating cardiac size has been widely popularized in clinical work because of its simplicity. Many workers feel that the assumption that the transverse diameter of the heart should be less than half the internal diameter of the chest is too crude to rule out cardiac enlargement since, in most people, the ratio will normally be considerably less than 0.50. It will be seen in Table II that the

TABLE IV

MEAN VALUES AND RANGE OF DISTRIBUTION OF CARDIO-THORACIC RATIOS* CALCULATED FROM 3159 ROENTGENOGRAPHIC EXAMINATIONS ON 71 BOYS AND 57 GIRLS UNDER STUDY AT THE CHILD RESEARCH COUNCIL

Age (yr.)	Group	Number of measurements	Minimum	Mean	Maximum
4	Boys	130	0.35	0.44	0.50
	Girls	112	0.36	0.44	0.50
5	Boys	168	0.37	0.43	0.50
	Girls	126	0.37	0.43	0.49
6	Boys	174	0.36	0.43	0.48
	Girls	145	0.36	0.43	0.49
7	Boys	164	0.34	0.42	0.50
	Girls	147	0.35	0.43	0.49
8	Boys	169	0.35	0.42	0.49
	Girls	136	0.36	0.43	0.48
9	Boys	164	0.35	0.42	0.50
	Girls	117	0.35	0.42	0.50
10	Boys	149	0.35	0.41	0.49
	Girls	103	0.36	0.42	0.50
11	Boys	140	0.35	0.41	0.48
	Girls	98	0.34	0.42	0.49
12	Boys	134	0.34	0.41	0.47
	Girls	91	0.35	0.41	0.48
13	Boys	116	0.33	0.41	0.48
	Girls	88	0.34	0.41	0.47
14	Boys	90	0.34	0.40	0.48
	Girls	69	0.35	0.40	0.46
15	Boys	66	0.34	0.40	0.48
	Girls	40	0.35	0.41	0.47
16	Boys	45	0.32	0.40	0.48
	Girls	34	0.36	0.40	0.46
17	Boys	37	0.35	0.41	0.47
	Girls	21	0.35	0.40	0.46
18 & over	Boys	50	0.36	0.40	0.48
	Girls	28	0.35	0.40	0.45

* Cardio-thoracic Ratio $= \frac{\text{Transverse Diameter of Heart}}{\text{Internal Diameter of Chest}}$

correlation coefficients for transverse diameter of the heart and internal diameter of the chest, while not high, are at least no lower than the correlation coefficients for transverse diameter of the heart and body weight. The cardio-thoracic ratios were therefore calculated for each child. The mean values for each age are shown in Table IV along with the minimum and maximum values for both boys and girls. Mean values for the ratios drop from 0.44 at four years to 0.40 for the groups that were post-pubescent. The greatest ratios that were obtained were 0.50, and the lowest was 0.32.

TABLE V

MEAN VALUES FOR CARDIO-THORACIC RATIOS* FOR INDIVIDUALS SEPARATED INTO OVERWEIGHT, MEDIUM-WEIGHT OR UNDERWEIGHT GROUPS. MEASUREMENTS TAKEN FROM 3159 ROENTGENOGRAPHIC EXAMINATIONS ON 71 BOYS AND 57 GIRLS UNDER STUDY

Boys			Age (yr.)	Girls		
Overweight for height	Medium-wt. for height	Underweight for height		Overweight for height	Medium-wt. for height	Underweight for height
0.42	0.44	0.44	4	0.44	0.43	0.45
0.42	0.43	0.43	5	0.43	0.43	0.44
0.42	0.43	0.43	6	0.43	0.43	0.43
0.42	0.42	0.43	7	0.42	0.43	0.43
0.42	0.42	0.41	8	0.43	0.42	0.43
0.42	0.42	0.41	9	0.43	0.42	0.43
0.41	0.41	0.41	10	0.43	0.41	0.42
0.41	0.41	0.42	11	0.43	0.41	0.42
0.41	0.41	0.41	12	0.42	0.41	0.41
0.41	0.41	0.41	13	0.42	0.40	0.41
0.40	0.40	0.40	14	0.41	0.40	0.40
0.41	0.40	0.41	15	0.42	0.40	0.40
0.40	0.39	0.42	16	0.42	0.40	0.38
0.40	0.39	0.40	17	0.42	0.40	0.38
0.39	0.39	0.43	18 & over	0.40	0.41	0.38

* Cardio-thoracic Ratio $= \frac{\text{Transverse Diameter of Heart}}{\text{Internal Diameter of Chest}}$

The range, therefore, includes hearts with transverse diameter measurements that are half the internal diameter of the chest as well as those that are no more than one-third the chest width. No significant sex difference was seen. When the ratios for each individual were inspected, it was found that the usual range was about 0.10. That is, if the highest ratio for a child was 0.48 or 0.49, the lowest was usually not less than 0.39 or 0.40. Or if the lowest ratio was 0.34 or 0.35, the highest was usually not more than 0.44 or 0.45. While the higher ratios were not always found in earlier childhood, that was frequently the case. Thus it would seem that, in healthy children, the cardio-thoracic ratio does not exceed 0.50 on erect films on cooperative subjects. In the individual case, enough variation is seen on successive films to make it difficult, if not impossible, to set up a standard or average value for each child that would serve as his expected "normal." A sustained increase of that ratio on successive films would however, be suggestive of cardiac enlargement and might be more significant than actual cardiac measurements that were not related to the increase in size of the chest.

Since differences in the mean values for transverse diameter of the heart were

demonstrated for the children who were of different height-weight proportions, one wonders if differences can also be elicited in the cardio-thoracic ratios of the thin children, fat children, and the children of medium proportions. That there were none is seen in Table V where mean values for all three groups are tabulated. The same decrease from higher mean values at four years to lower means after adolescence is seen that was present in the mass data but apparently differences in height-weight

TABLE VI

COMPARISON OF MEASUREMENTS OF TRANSVERSE DIAMETER OF HEART FROM ROENTGENOGRAMS AND ESTIMATIONS FROM UNGERLEIDER'S NOMOGRAM.* FROM 777 ROENTGENOGRAPHIC EXAMINATIONS OF 50 BOYS AND 37 GIRLS UNDER STUDY AT THE CHILD RESEARCH COUNCIL

Age in Years	No.† of cases	Percentage Deviation of Predicted T.D. from Measured T.D.‡									
		−10% through −14%	−5% through −9%	−1% through −4%	0%	+1% through +4%	+5% through +9%	+10% through +14%	+15% through +19%	+20% through +24%	+25% through +29%
Boys											
11 & 12	50	2% of cases	6% of cases	12% of cases	10% of cases	20% of cases	16% of cases	16% of cases	14% of cases	4% of cases	—
13	83	—	4%	11%	10%	27%	13%	24%	10%	1%	—
14	89	1%	2%	9%	3%	22%	28%	21%	9%	3%	—
15	70	—	3%	8%	7%	21%	30%	20%	10%	—	—
16	46	—	2%	9%	13%	22%	28%	15%	7%	2%	2%
17	39	—	3%	10%	3%	15%	49%	13%	5%	3%	—
18 and over	44	—	2%	11%	4%	25%	30%	27%	—	—	—
Girls											
10 & 11	40	—	—	7.5%	2.5%	7.5%	45.0%	30.0%	2.5%	5.0%	
12	52	—	8%	2%	4%	23%	25%	17%	19%	2%	—
13	72	—	3%	6%	4%	15%	26%	19%	22%	4%	—
14	69	—	—	4%	10%	19%	19%	20%	19%	9%	—
15	41	—	—	7%	7%	17%	15%	29%	15%	10%	—
16	33	—	—	9%	—	21%	21%	27%	18%	3%	—
17	21	—	—	5%	—	24%	28%	14%	24%	5%	—
18	28	—	—	4%	—	11%	39%	14%	14%	11%	7%
Totals:											
Girls	356	—	2%	5%	4%	17%	26%	22%	17%	6%	1%
Boys	421	0.5%	3%	10%	7%	23%	26%	20%	8%	2%	0.2%
Boys & girls	777	0.3%	2%	8%	6%	20%	26%	21%	12%	4%	0.4%

* Predictive values for transverse diameter of heart are estimated from Ungerleider's Nomogram based on height and weight.[1]

† No. of cases refers to number of examinations for each age period rather than to number of individuals.

‡ Percentage Deviation = $\frac{\text{Predicted T.D.} - \text{Measured T.D.} \times 100}{\text{Predicted T.D.}}$

relationships are equalized by changes in the chest width so that the cardio-thoracic ratios are not altered in any one group. There is a suggestion of smaller ratios in the thin post-adolescent girls than in the fat post-adolescent girls but this is reversed in the thin post-adolescent boys. Since the transverse diameter of the heart is smaller in the thin post-adolescent boys, the larger cardio-thoracic ratios in this group must be a reflection of disproportionately narrower chests.

Prediction tables or nomograms for cardiac size based on easily obtained body measurements have been worked out by various investigators in recent years. One of the most widely used nomograms for adults is that constructed by Ungerleider.[1] He does not suggest that the nomogram is applicable in the adolescent period but it seemed worthwhile to compare the predicted and actual values for transverse diameter of the heart to get an indication of how useful it might be for these ages, since many of our adolescent

TABLE VII

INDIVIDUAL MEASUREMENTS ON BOYS*

Subject	Age yr.	Age mo.	T.D. (cm.)	L.D. (cm.)	B.D. (cm.)	I.D. (cm.)	Ht. (cm.)	Wt. (kg.)	T.D./I.D.
#34	5	11	7.60	8.60	6.80	17.90	112.40	17.10	0.42
	6	5	8.40	9.05	7.45	18.30	116.80	19.20	0.46
	6	11	8.25	9.50	7.25	18.70	119.40	19.60	0.44
	7	5	8.45	9.55	7.45	19.30	121.90	21.20	0.44
	7	11	8.35	9.50	7.85	19.30	126.70	22.00	0.43
	8	6	8.70	9.60	7.85	19.80	127.00	23.30	0.44
	9	1	8.75	9.50	8.20	19.70	130.30	24.00	0.44
	9	8	8.70	9.90	8.00	20.00	133.00	25.90	0.44
	10	1	9.00	10.05	8.65	20.10	135.30	26.30	0.45
	10	7	9.80	10.85	8.75	21.30	137.80	28.80	0.46
	11	3	9.80	11.05	8.95	21.40	141.90	30.50	0.46
	11	9	8.95	9.95	8.80	21.60	143.80	30.90	0.41
	12	0	8.70	9.95	8.55	21.70	145.10	32.10	0.40
	12	6	9.55	10.40	8.90	22.20	147.00	35.00	0.43
	13	0	10.25	11.30	9.55	22.40	149.60	37.80	0.46
	13	6	10.15	10.85	9.35	23.20	156.80	40.90	0.44
	14	0	10.50	11.60	10.60	24.00	160.40	42.00	0.44
	14	6	11.05	11.90	10.20	24.90	165.60	49.70	0.44
	15	0	11.00	12.20	10.90	25.10	168.20	50.90	0.44
	15	6	11.80	13.00	11.00	25.90	170.70	55.80	0.46
	16	0	11.60	12.75	10.75	26.10	171.40	56.80	0.44
	16	6	11.60	12.65	11.00	26.30	171.80	59.40	0.44
	17	0	11.70	12.75	11.30	26.80	172.40	60.70	0.44
	19	0	11.45	12.20	10.50	26.50	172.50	61.80	0.43
#19	9	6	8.30	9.40	7.65	22.20	135.30	28.50	0.37
	9	10	8.95	9.75	7.90	22.20	133.70	29.90	0.40
	10	1	8.80	9.80	7.90	22.60	137.90	30.10	0.39
	10	3	9.45	10.35	8.50	22.70	137.90	31.00	0.42
	10	6	8.65	9.60	7.85	22.90	139.10	30.50	0.38
	10	9	9.55	10.50	8.65	23.00	140.30	31.60	0.40
	11	0	9.80	10.90	8.70	23.20	141.60	31.80	0.42
	11	3	9.55	10.75	8.20	23.40	143.50	33.40	0.41
	11	7	9.15	10.30	8.20	22.90	144.80	34.60	0.40
	11	9	9.90	10.70	8.80	23.10	144.80	34.60	0.43
	12	0	10.05	11.00	8.80	23.80	146.70	35.40	0.42
	12	5	9.65	10.60	8.75	24.10	149.20	36.70	0.40
	12	8	9.10	10.40	8.75	24.20	151.80	37.20	0.38
	13	0	9.75	10.60	8.90	24.50	153.00	39.30	0.40
	13	3	10.30	11.25	9.00	—	154.90	41.00	—
	13	6	10.55	11.50	9.40	26.10	157.50	43.10	0.40
	13	9	10.55	11.70	9.50	26.00	158.80	44.80	0.40
	14	0	11.25	12.25	9.80	27.00	161.90	47.50	0.42
	14	3	10.70	11.45	9.15	27.90	163.80	49.70	0.38
	14	6	10.95	12.10	9.60	28.10	165.10	52.50	0.39
	14	9	11.15	12.20	9.85	28.30	166.40	52.70	0.39
	15	0	11.70	12.75	9.95	28.70	168.30	53.80	0.41
	15	3	11.45	12.50	10.25	28.10	170.50	55.70	0.41
	15	6	11.55	12.55	10.00	28.60	170.50	55.90	0.40
	15	9	11.60	12.95	10.75	28.90	173.50	57.70	0.40

TABLE VII—(*continued*)

Subject	Age yr.	Age mo.	T.D. (cm.)	L.D. (cm.)	B.D. (cm.)	I.D. (cm.)	Ht. (cm.)	Wt. (kg.)	T.D. / I.D.
	16	0	11.30	12.80	10.20	29.20	174.00	58.30	0.39
	16	3	11.35	12.90	10.30	29.20	174.30	58.30	0.39
	16	6	11.70	13.20	10.60	29.10	174.30	58.60	0.40
	16	9	10.85	12.10	9.95	29.50	174.30	60.20	0.37
	17	0	10.80	12.05	9.90	29.40	174.60	59.50	0.37
	17	3	10.85	12.25	10.25	29.60	174.90	59.20	0.37
	17	6	11.70	13.15	10.65	29.60	174.90	60.10	0.39
	17	11	11.70	13.05	10.60	29.90	170.80	63.30	0.39
	18	11	12.00	13.20	10.55	30.10	171.30	62.80	0.40
	20	0	10.95	12.75	10.10	30.50	171.60	60.10	0.36
	21	0	11.45	12.90	10.50	30.40	—	—	0.38
	21	3	11.40	13.15	10.25	30:30	171.00	61.20	0.38
	21	8	11.40	13.10	10.35	30.20	—	—	0.38
	22	0	10.85	12.55	10.00	30.40	170.90	60.80	0.36
	22	3	11.50	12.90	10.40	30.40	—	—	0.38
	22	3	11.75	13.25	10.90	30.60	—	—	0.38
#30	9	0	8.00	9.80	8.15	21.20	139.10	28.50	0.38
	9	3	8.10	9.80	8.10	20.90	140.30	29.80	0.39
	9	6	8.65	9.80	8.45	22.20	140.30	30.80	0.39
	9	9	7.95	9.30	8.50	21.30	141.00	31.80	0.37
	10	0	8.35	10.20	8.25	22.40	142.90	32.20	0.37
	10	3	8.50	9.75	8.70	22.00	145.40	32.00	0.39
	10	6	8.90	10.35	8.40	21.60	146.70	34.70	0.41
	10	9	9.35	10.70	8.90	22.80	148.60	34.60	0.41
	11	0	9.50	11.10	9.10	23.00	149.20	35.90	0.41
	11	3	8.80	10.50	9.05	22.90	150.70	35.10	0.38
	11	6	8.75	10.55	8.85	22.70	151.80	36.70	0.39
	11	9	9.45	11.10	9.15	23.60	153.70	37.80	0.40
	12	0	9.80	11.10	9.20	23.50	—	—	0.42
	12	3	9.70	11.00	9.30	23.80	154.90	36.90	0.41
	12	6	10.25	11.60	9.45	23.50	156.20	40.60	0.44
	12	9	9.85	11.65	9.20	23.80	157.50	41.00	0.41
	13	0	9.90	10.80	9.60	24.60	159.40	43.60	0.40
	13	3	9.80	11.30	9.40	24.90	160.00	41.70	0.39
	13	6	9.65	11.60	9.50	24.50	161.30	46.00	0.39
	13	9	10.50	11.90	9.70	25.90	163.80	48.60	0.40
	14	0	10.20	11.40	9.70	26.10	166.40	45.70	0.39
	14	3	10.25	11.35	9.75	26.40	168.90	49.20	0.39
	14	6	11.60	12.90	10.50	26.90	169.80	54.00	0.43
	14	9	11.35	12.40	10.60	27.20	172.70	56.00	0.42
	15	0	10.80	12.00	10.30	27.90	175.30	58.10	0.39
	15	3	10.70	11.80	10.00	27.60	175.90	59.20	0.39
	15	6	10.70	12.00	10.45	27.50	177.20	59.10	0.39
	15	9	10.65	12.60	10.15	27.80	178.10	59.60	0.38
	16	0	11.20	12.40	10.20	28.10	179.10	61.80	0.40
	16	3	11.10	12.45	10.45	27.90	179.70	62.70	0.40
	16	6	11.70	13.30	10.75	28.40	180.60	64.70	0.41
	16	9	11.05	12.65	10.75	28.40	181.00	65.60	0.39
	17	0	11.05	12.30	10.30	28.60	181.60	66.40	0.39
	17	3	11.30	12.75	10.60	28.80	180.20	66.60	0.39

TABLE VII—(*continued*)

Subject	Age yr.	Age mo.	T.D. (cm.)	L.D. (cm.)	B.D. (cm.)	I.D. (cm.)	Ht. (cm.)	Wt. (kg.)	T.D./I.D.
	18	0	10.90	12.15	10.05	28.50	180.40	66.10	0.38
	19	0	10.80	12.15	10.40	28.90	181.20	70.00	0.37
	19	10	10.90	12.40	10.40	28.70	181.40	70.20	0.38
	21	0	11.40	12.60	10.80	28.90	181.60	77.80	0.39
#56	4	9	8.15	8.90	6.85	18.00	109.90	19.00	0.45
	4	11	8.70	9.20	7.35	18.60	111.10	20.60	0.47
	5	2	8.85	9.25	7.55	18.80	113.00	21.30	0.47
	5	7	8.25	8.95	7.10	18.80	116.50	21.20	0.44
	5	11	9.15	9.60	7.40	19.20	119.40	23.00	0.48
	6	2	8.65	9.60	7.45	19.30	121.90	23.50	0.47
	6	5	8.70	9.30	7.55	19.50	123.20	23.90	0.45
	6	8	8.80	9.00	7.50	20.00	124.80	24.60	0.44
	6	11	8.85	9.55	7.55	19.70	126.40	25.70	0.45
	7	2	9.35	10.15	8.05	19.90	127.60	26.90	0.47
	7	5	8.25	9.20	8.05	20.40	130.20	26.80	0.41
	7	8	8.90	9.60	8.55	20.10	132.10	26.70	0.44
	8	0	9.15	9.70	8.20	20.90	134.00	27.30	0.44
	8	2	9.55	9.90	8.55	20.70	134.60	28.60	0.46
	8	6	9.80	10.15	8.60	20.90	136.80	29.90	0.47
	8	9	9.15	10.00	8.25	20.80	138.40	30.50	0.44
	8	11	9.00	9.50	8.20	21.30	139.70	31.30	0.42
	9	2	9.75	10.60	8.50	21.10	141.60	32.20	0.46
	9	5	8.85	9.60	7.75	21.60	141.60	32.10	0.41
	9	8	9.35	10.35	8.70	21.50	144.20	33.10	0.43
	10	0	9.45	10.00	8.60	21.90	144.80	35.30	0.43
	10	3	10.65	11.20	9.50	21.90	145.70	36.10	0.49
	10	6	9.60	10.60	8.60	22.00	149.20	37.60	0.44
	10	9	9.70	10.45	8.60	22.50	148.20	38.00	0.43
	11	0	10.45	11.50	9.20	22.50	149.20	40.40	0.46
	11	6	10.60	11.30	9.05	23.00	152.30	40.50	0.46
	12	0	10.35	11.20	8.85	23.10	155.00	41.80	0.45
	12	6	10.85	11.55	9.60	23.30	157.00	46.20	0.47
	13	0	10.75	11.60	10.00	23.60	160.10	46.00	0.45
	13	6	11.10	11.75	10.05	23.90	162.20	48.90	0.46
	14	0	10.60	11.45	9.85	24.90	166.40	52.00	0.43
	14	6	9.40	10.60	9.05	25.20	173.20	54.50	0.37
	15	0	9.30	10.05	8.70	25.20	176.50	58.70	0.37
	15	6	9.90	10.90	9.95	26.80	179.80	63.30	0.37

* T.D. = Transverse Diameter of heart measured from roentgenogram
L.D. = Long Diameter of heart measured from roentgenogram
B.D. = Broad Diameter of heart measured from roentgenogram
I.D. = Internal Diameter of chest measured from roentgenogram
Ht. = Height at time of roentgenographic examination. Apparent loss of height for some older subjects is attributable to a change in measuring instruments during accumulation of these data.
Wt. = Weight at time of roentgenographic examination

$$\frac{\text{T.D.}}{\text{I.D.}} = \frac{\text{Transverse Diameter of Heart}}{\text{Internal Diameter of Chest}}$$

TABLE VIII

INDIVIDUAL MEASUREMENTS ON GIRLS*

Subject	Age yr.	Age mo.	T.D. (cm.)	L.D. (cm.)	B.D. (cm.)	I.D. (cm.)	Ht. (cm.)	Wt. (kg.)	T.D. / I.D.
# 1	6	0	7.80	8.30	6.80	18.70	110.50	17.00	0.42
	6	3	8.30	8.90	7.00	18.60	112.40	16.90	0.45
	6	6	7.70	8.45	7.20	18.80	113.70	16.90	0.41
	6	9	7.85	8.25	6.90	19.00	114.30	18.10	0.41
	7	0	8.35	8.55	7.00	19.10	116.20	18.60	0.44
	7	2	8.20	8.70	7.20	19.00	117.50	19.30	0.43
	7	6	8.60	9.00	7.40	19.40	118.70	20.40	0.44
	7	9	8.90	9.60	7.30	19.60	120.00	21.40	0.45
	8	0	8.95	9.40	7.20	19.50	121.90	22.20	0.46
	8	3	7.80	8.80	7.35	19.15	121.90	21.90	0.41
	8	6	7.85	8.45	7.10	19.80	124.10	22.60	0.40
	9	2	8.10	8.50	6.95	20.20	127.60	23.70	0.40
	9	6	8.80	9.25	7.75	20.20	129.50	24.30	0.44
	9	9	8.40	9.10	7.65	20.00	130.20	25.20	0.42
	10	0	8.40	8.90	7.70	20.50	130.80	25.90	0.41
	10	4	8.30	8.90	7.75	21.00	132.10	25.90	0.40
	10	7	8.35	9.05	8.00	20.70	133.40	27.30	0.40
	10	10	8.50	9.20	7.75	21.00	134.90	27.60	0.40
	11	1	8.85	9.45	7.80	21.10	135.90	27.30	0.42
	11	5	8.70	9.30	8.10	21.40	137.20	28.80	0.41
	11	9	8.80	9.40	8.10	21.40	139.10	29.10	0.41
	12	0	8.80	9.55	8.40	21.55	141.60	30.40	0.41
	12	3	8.40	9.35	8.30	21.50	142.50	30.60	0.39
	12	6	8.90	9.75	8.80	22.00	144.40	31.80	0.40
	12	9	8.80	9.60	8.45	21.80	146.00	32.80	0.40
	13	0	9.60	10.30	8.75	22.15	147.30	34.20	0.43
	13	3	9.30	10.25	9.05	22.80	149.20	34.60	0.41
	13	6	10.05	10.85	9.35	22.70	151.10	37.00	0.44
	13	9	10.40	11.10	9.35	22.65	153.00	39.20	0.46
	14	0	9.55	10.30	9.25	23.80	156.80	42.40	0.40
	14	3	9.70	10.50	9.30	23.60	157.80	42.20	0.41
	14	6	9.20	10.10	8.65	23.90	155.10	40.50	0.39
	15	0	9.40	10.40	9.25	23.70	157.50	40.40	0.40
	15	6	10.00	11.00	9.20	22.10	158.70	40.50	0.45
	16	0	9.10	10.40	9.25	23.30	159.00	41.90	0.39
	16	6	8.85	9.80	9.05	23.50	159.20	41.10	0.38
	17	1	9.30	10.65	9.55	23.60	159.30	40.00	0.39
	18	0	9.30	10.45	9.70	23.80	160.00	41.50	0.39
	19	1	9.20	10.15	9.10	23.60	160.00	43.70	0.39
#53	5	9	7.80	8.80	7.20	18.80	115.60	19.50	0.41
	6	0	8.05	9.00	7.40	18.80	116.20	19.50	0.43
	6	3	8.40	9.15	7.35	19.40	118.80	20.40	0.43
	6	6	7.60	8.45	7.00	19.40	120.60	21.00	0.39
	6	9	7.65	8.85	7.55	19.80	120.60	22.20	0.39
	7	0	8.10	9.40	7.75	19.80	123.80	22.00	0.41
	7	3	8.10	9.25	7.55	19.90	125.70	21.70	0.41
	7	6	8.35	9.45	7.85	20.10	127.60	23.90	0.42
	7	9	9.00	9.80	7.85	20.00	128.90	25.00	0.45
	8	0	8.05	8.85	6.65	19.70	129.50	21.90	0.41
	8	3	8.35	9.35	7.20	20.30	131.40	25.00	0.41
	8	6	8.55	9.50	7.25	20.10	133.60	26.80	0.42
	8	9	8.55	9.50	7.65	21.00	134.90	28.50	0.41
	9	0	9.15	10.30	8.05	21.30	136.50	28.30	0.43
	9	4	8.85	10.05	7.85	21.60	138.40	29.40	0.41

TABLE VIII—(*continued*)

Subject	Age yr.	Age mo.	T.D. (cm.)	L.D. (cm.)	B.D. (cm.)	I.D. (cm.)	Ht. (cm.)	Wt. (kg.)	T.D. / I.D.
	9	7	9.55	10.85	8.30	21.60	140.00	30.80	0.44
	9	10	9.00	10.20	8.15	21.60	141.60	32.60	0.42
	10	1	9.70	10.80	8.40	22.00	142.90	32.10	0.44
	10	4	9.60	11.00	8.40	22.00	144.80	32.10	0.44
	10	7	9.60	11.00	8.65	22.40	146.00	33.90	0.43
	10	10	9.60	11.10	8.75	22.20	148.00	34.80	0.43
	11	0	10.25	11.75	9.05	22.80	149.20	35.70	0.45
	11	3	9.90	11.45	8.80	23.10	151.40	36.30	0.43
	11	6	10.20	11.60	9.05	23.40	154.00	38.20	0.44
	11	10	9.70	11.15	8.70	23.60	156.50	40.50	0.41
	12	0	9.90	11.70	9.05	23.90	159.40	41.60	0.42
	12	3	9.85	11.10	8.50	24.50	160.30	43.10	0.40
	12	6	10.40	11.95	9.25	24.70	162.60	45.40	0.42
	12	9	10.50	12.30	9.65	25.00	163.80	48.00	0.42
	13	0	10.45	11.95	9.75	25.20	164.50	49.20	0.41
	13	6	10.85	12.30	9.25	25.50	166.70	51.80	0.42
	14	0	11.15	12.50	10.15	25.60	166.20	54.00	0.43
	14	7	10.35	11.90	9.45	25.70	167.10	52.90	0.40
	15	0	11.15	12.50	9.75	26.20	168.00	55.30	0.42
	16	0	11.05	12.40	10.15	25.60	168.70	55.30	0.43
	17	0	11.00	12.70	10.00	26.10	168.90	55.10	0.42
	18	10	11.45	13.00	11.20	26.30	168.80	57.60	0.44
#43	3	9	8.30	8.85	7.60	18.50	105.40	16.60	0.45
	4	0	8.20	8.85	7.50	19.00	106.00	17.10	0.43
	4	3	8.30	8.90	7.45	18.90	108.00	17.60	0.44
	4	6	8.30	8.90	7.55	19.30	110.50	18.50	0.43
	4	9	8.30	8.95	7.85	19.50	110.80	18.50	0.43
	5	0	7.85	8.65	7.35	19.50	114.30	19.50	0.40
	5	3	8.25	9.00	7.95	19.50	115.60	20.40	0.42
	5	8	8.55	9.40	8.15	20.20	119.40	21.40	0.42
	6	1	8.65	9.45	7.95	20.40	121.90	22.10	0.42
	6	4	8.90	9.60	8.30	20.40	124.20	23.00	0.44
	6	7	7.95	9.05	7.70	20.60	124.80	22.30	0.39
	6	10	8.05	9.05	7.55	20.90	127.00	24.50	0.39
	7	1	7.65	8.45	7.20	21.00	127.60	24.40	0.36
	7	4	7.95	8.75	7.85	21.30	129.50	25.90	0.37
	7	7	8.20	9.15	7.75	20.60	131.40	26.70	0.40
	7	9	8.05	8.80	7.70	21.50	133.40	25.90	0.37
	8	1	8.40	9.40	8.15	21.70	135.30	28.10	0.39
	8	3	8.55	9.50	7.85	22.20	135.90	28.20	0.39
	8	6	9.60	10.15	8.70	21.40	137.50	29.80	0.45
	8	10	9.30	10.40	8.85	22.10	139.70	29.60	0.42
	9	1	8.85	9.75	8.50	22.10	140.30	30.90	0.40
	9	3	8.70	9.80	8.60	21.50	141.60	32.20	0.40
	9	6	9.25	10.55	9.15	22.50	143.20	33.60	0.41
	9	9	8.55	9.85	8.60	22.30	144.20	35.00	0.38
	10	0	8.85	10.10	8.60	22.40	146.70	37.00	0.40
	10	3	9.70	11.10	9.20	23.20	148.00	38.20	0.42
	10	6	9.35	10.55	8.65	23.10	148.90	40.90	0.40
	10	9	9.15	10.40	8.85	23.40	150.50	41.40	0.39
	11	1	9.00	10.70	8.80	24.00	151.80	42.20	0.38
	11	3	9.70	11.15	9.20	24.00	154.90	43.90	0.40
	11	6	9.15	10.90	9.05	24.10	157.20	45.50	0.38
	11	9	9.85	11.35	9.30	25.00	156.80	47.40	0.39
	12	0	11.00	12.25	10.35	25.50	157.90	49.10	0.43

TABLE VIII—(*continued*)

Subject	Age yr.	Age mo.	T.D. (cm.)	L.D. (cm.)	B.D. (cm.)	I.D. (cm.)	Ht. (cm.)	Wt. (kg.)	T.D./I.D.
	12	6	9.55	11.25	9.40	25.80	161.50	50.00	0.37
	13	0	8.75	10.60	8.95	25.20	163.80	51.90	0.35
	13	6	9.20	10.95	9.20	26.50	165.40	51.80	0.35
	14	0	10.30	12.05	9.60	26.50	166.40	53.10	0.39
	14	6	9.70	11.45	9.50	26.60	167.50	54.20	0.36
	15	1	10.30	11.95	10.30	25.50	167.80	55.60	0.40
	15	6	10.65	12.40	10.15	25.70	168.20	56.70	0.41
	16	0	10.60	12.25	10.20	26.30	168.70	56.10	0.40
# 2	4	10	7.90	8.80	7.35	18.10	102.90	14.10	0.44
	5	1	7.10	8.00	6.40	16.90	104.10	14.40	0.42
	5	4	7.70	8.30	6.65	18.05	105.40	14.40	0.43
	5	7	7.55	8.30	6.85	18.20	106.70	15.00	0.41
	6	3	7.40	8.30	6.70	18.60	110.50	15.60	0.40
	6	6	8.30	8.90	6.90	18.50	112.10	16.20	0.45
	6	9	8.30	9.20	7.20	18.80	113.30	16.80	0.44
	7	0	7.60	8.65	6.85	18.80	114.60	17.40	0.40
	7	5	8.30	9.30	7.30	19.00	116.20	17.20	0.44
	7	8	8.25	9.25	7.55	19.20	118.70	18.10	0.43
	7	10	8.00	9.30	7.40	18.70	119.70	17.80	0.43
	8	2	8.00	9.30	7.30	19.20	120.60	18.10	0.42
	8	5	8.40	9.55	7.45	19.30	122.90	18.60	0.44
	8	9	7.85	9.15	7.60	19.60	123.80	19.30	0.42
	9	0	8.20	9.70	7.80	19.70	125.10	19.50	0.44
	9	3	8.40	9.50	7.80	19.40	126.70	19.80	0.43
	9	9	8.20	9.60	7.65	19.50	128.60	20.50	0.42
	10	0	8.80	9.90	7.70	19.50	128.60	21.40	0.45
	10	3	7.80	9.35	7.55	19.70	130.80	21.10	0.40
	10	6	7.90	9.05	7.50	20.00	131.80	22.20	0.40
	10	9	8.40	9.70	7.85	19.90	134.90	22.80	0.42
	11	0	8.70	9.80	7.95	20.20	135.30	24.20	0.43
	11	3	8.60	9.70	8.20	19.90	135.90	23.10	0.43
	11	6	8.75	9.85	7.80	20.30	134.50	23.50	0.43
	11	9	8.60	9.95	8.10	20.50	137.00	23.70	0.42
	12	0	8.10	9.50	8.00	20.40	138.00	24.00	0.40
	12	5	8.60	9.50	7.75	20.80	140.30	24.30	0.41
	12	6	8.70	9.90	8.10	21.10	140.60	25.60	0.41
	13	0	8.70	10.05	8.30	21.40	143.60	27.10	0.41
	13	6	8.40	9.85	8.30	21.50	147.30	28.60	0.39
	14	0	9.00	10.40	8.95	22.50	150.90	31.10	0.40
	14	6	8.80	10.40	8.25	22.80	153.50	32.10	0.39
	15	0	9.15	10.65	8.80	23.20	154.60	33.20	0.39
	16	0	8.35	10.30	8.65	23.20	156.60	34.20	0.36

* T.D. = Transverse Diameter of heart measured from roentgenogram
L.D. = Long Diameter of heart measured from roentgenogram
B.D. = Broad Diameter of heart measured from roentgenogram
I.D. = Internal Diameter of chest measured from roentgenogram
Ht. = Height at time of roentgenographic examination. Loss of height for some older subjects is attributable to a change in measuring instruments during accumulation of these data.
Wt. = Weight at time of roentgenographic examination

$$\frac{\text{T.D.}}{\text{I.D.}} = \frac{\text{Transverse Diameter of Heart}}{\text{Internal Diameter of Chest}}$$

and post-adolescent boys and girls had heights and weights that would allow such prediction. In our Child Research Council series there were 777 such measurements available for comparison—421 on boys and 356 on girls who ranged in age from 10 years to over 22 years with the greatest number of measurements at the 13, 14, and 15 year levels. Eighty percent of the predicted transverse diameters of the heart exceeded the measured values. There was no better agreement in the later ages than in the earlier. Nor was there any difference in the agreement for the fat, medium, or thin groups. Nearly half the predicted values exceeded the actual by over 10% as is seen in Table VI. It would seem, therefore, that this nomogram might need some modification before it can be used in the later childhood and early adult periods.

Summary

As part of a longitudinal study of healthy children by the staff of the Child Research Council, roentgenograms of the chest have been made at frequent intervals. Three cardiac diameters (transverse, long, and broad) and the internal diameter of the chest were measured on each of 3205 of these roentgenograms, taken of 128 subjects over a period of years.

The size and shape of the heart are illustrated and discussed with emphasis on the range of variation that is seen in healthy individuals and on the inadequacy of one set of "normal standards" for evaluating the cardiac silhouette.

In spite of fluctuations in the growth curves for the cardiac diameters, a general pattern of agreement was found in the increases in the cardiac diameters and the increases in body height and weight during childhood and adolescence. It would seem that periods of rapid growth such as are usually seen in adolescence are frequently coincident with fairly rapid increases in the cardiac diameters, suggesting that cardiac demands are greater during such growth spurts.

The mean values for transverse diameter of the heart showed the same type of sex differentiation that is found in the mean values for height and weight in boys and girls. It seems logical to assume that changing cardiac size should be considered as part of the growth process rather than as an isolated physical and physiologic process.

The relations that seem apparent between transverse diameter of the heart and height, weight, and internal diameter of the chest could not be proved statistically by calculated coefficients of correlation. However, it was possible to show differences in the mean values for cardiac transverse diameter in three groups, classified as to height-weight relationships into overweight, medium-weight, and underweight individuals. The mean values were greatest for the fat group, least for the thin group and intermediate for the group that was of medium weight for height. Body build may therefore be a factor in determining cardiac size during childhood as well as during adolescence and adult life.

Since the width of the chest is increasing during childhood and adolescence in much the same manner that the transverse diameter of the heart is increasing, cardio-thoracic ratios do not become progressively greater with advancing age. In fact, the successive ratios on the same individual show little regularity toward either increase or decrease although mean values for the different ages do decrease from a high of 0.44 at four years of age to a low of 0.40 in the post-adolescent age groups. Each individual showed considerable fluctuation in the cardio-thoracic ratios but no one person fluctuated as much as the range for the whole group. No ratios were found above 0.50 or below 0.32. No sex differences were found nor was there any significant dif-

ference in the cardio-thoracic ratios for the groups of different height-weight proportions. In evaluating the heart size of an individual from a single film, the cardio-thoracic ratio is probably as satisfactory as any other measurement if one recognizes the wide range of healthy variation. An increase in the cardio-thoracic ratio on successive roentgenograms might be more significant clinically than cardiac measurements which did not take into consideration the growth of the individual.

The nomogram constructed by Ungerleider based on height and weight for prediction of transverse diameter of the heart on teleoroentgenograms of adults was tested for its applicability to the later childhood, adolescent and early adult periods. Nearly half the predicted cardiac transverse diameters exceeded the measured values by 10% or more.

This study would seem to indicate, therefore, that one should not be discouraged by the range of variation or the fluctuations in cardiac measurements from routine roentgenograms of the chest. Valuable information regarding the significance of the size of the heart can be obtained from such roentgenograms if one relates those data to the basic process of growth and maturation of the individual.

ACKNOWLEDGEMENT

The work of Isabelle D. Truscott with the statistical analyses of these data is gratefully acknowledged.

REFERENCE

1. Ungerleider, H. E., and Gubner, R., Evaluation of heart size measurements, Am. Heart J. **24**:494, 1942.

SPANISH ABSTRACT

Crecimiento del Corazón con relación al Crecimiento del Cuerpo durante la Niñez y la Adolescencia

Se les midieron a ciento veintiocho niños los diámetros cardíacos (transversal, largo, ancho) y el diámetro interno del pecho con roentgenogramas serie 3205 tomados de los períodos de la niñez, adolescencia y temprana vida adulta. Como estos niños son parte de un estudio longitudinal de niños sanos, los altos y pesos se encontraban disponibles. Se trató de los tamaños y formas de los corazones sanos, poniendo énfasis en el grado de variabilidad en los diferentes niños y en la constancia de la forma cardíaca en cada individuo. Los diámetros mostraron fluctuación, pero se encontró un patrón general entre los aumentos en estos diámetros y el alto y peso durante la niñez y adolescencia. Períodos de crecimiento rápido visto en la adolescencia coincidían frecuentemente con aumentos rápidos en diámetros. Tales crecimientos parecen imponer mayores exigencias cardíacas y, por consiguiente, mayor tamaño. Como los grados medios del diámetro transversal muestran la misma diferenciación que se encuentra en los grados crecientes de alto y peso, el cambio del tamaño cardíaco está logicamente más bien considerado parte del proceso de crecimiento que un proceso físico aislado o fisiológico.

El acuerdo aparente entre los tamaños del corazón y del cuerpo no se puede probar por medio de coeficientes de correlación. Que la relación alto-peso pueda ser un factor en el tamaño fué indicado porque las diferencias entre los grados medios del diámetro transversal fueron demostradas cuando se separaron los niños en tres grupos; los que pesaban demasiado, los que no pesaben lo suficiente y los que tenían peso medio para su tamaño. Los grados medios fueron más grandes en el grupo de los de sobrepeso y más pequeños en los que no pesaban lo suficiente.

Como las proporciones cardio-torácicas se usan para determinar el tamaño del corazón, éstas fueron calculadas. Corrían de 0.32 a 0.50 y los grados medios mostraron una disminución gradual de 0.44 de alto a los cuatro años a 0.40 bajo en los grupos después de la edad de pubertad. No se encontró diferencia de sexo en estas proporciones, ni en los grupos con diferente relación alto-peso.

El diámetro transversal predicho del corazón, tal como fué leído en el nomograma construído por Ungerleider, excedió los grados medidos en los últimos años de la niñez, la adolescencia y los primeros años del período adulto.

4200 E. 9th Ave.

PSYCHOTHERAPEUTIC ASPECTS OF PEDIATRIC PRACTICE

By HILDE BRUCH, M.D., and DONOVAN J. MCCUNE, M.D.
New York, N.Y.

THE profound importance of emotional influences for the healthy or abnormal development of children is now generally recognized. Knowledge of this fact is so widespread, indeed, that one can scarcely open a medical journal or popular magazine without being confronted with it. This cartoon illustrates the fate of maldevelopment. It shows father, mother, sister and brother—all of them at once—under psychoanalytic treatment. The caption explains that a neurosis has its basis in conflicts within the family group. One might well raise the question: "Why did things go wrong to such an extent? Couldn't their pediatrician have advised them so that at least the children would have remained well?" This is a troublesome question from the point of view of both the psychiatrist and the pediatrician.

Psychiatrists have been very articulate in talking about the need for better emotional care but frequently the pediatrician has been left in a state of doubt and frustration. There has been too much emphasis on psychiatric methods from the psychiatrist's point of view and too little attention has been paid to the psychotherapeutic possibilities that are inherent in the practice of pediatrics.

The conventional and most fascinating way of demonstrating the importance of psychologic factors is the extensive case history which tells in detail all the vicissitudes of a child's emotional development and how the psycho-dynamics of his inner life are related to the many complaints and symptoms which had been resistant to traditional medical treatment.

The usefulness of such accounts for the pediatrician is their demonstration of what psychiatry can do and what patients might benefit from psychiatric treatment. Yet this treatment is time consuming and it requires special training and experience and it cannot be part of the practice of pediatrics.

Another way in which psychiatric thinking has influenced pediatric practice is in emphasizing the emotional significance of the ways and methods in which the infant's physiologic needs are fulfilled. Pediatrics is gradually emerging from the so-called scientific era of strict formulas, rigid schedules and absolute asepsis. The infant's needs for affection and close human contact are again being given their natural place and are admitted on an equal footing with calories and cleanliness in a doctor's recommendations to a mother.

As a matter of fact, in many ways a complete reversal is taking place. We hear now discussions of the relative merits of self-demand versus schedule feeding, of rooming-in versus the aseptic nursery, of a permissive attitude about letting a child learn toilet habits versus strict training at a preordained age. There can be no doubt that this new approach of taking clues for a child's care from his expressed needs and his readiness

From the Departments of Psychiatry and Pediatrics, College of Physicians and Surgeons, Columbia University.

Read at the Annual Meeting of the American Pediatric Society, Quebec, May 24, 1948.
(Received for publication May 25, 1948.)

to face new developmental challenges is a valuable step towards better emotional health. Yet the way in which the rediscovered natural approach is often handled carries dangers of its own.

It is my impression that failures of a fundamentally sound approach may be due to

By Permission. Copyright 1948 *The New Yorker Magazine,* Inc.

"Now, as I've said before, a neurosis often has its basis in conflicts within the family group."

intrinsic misinterpretations. There is a tendency to consider new insights and observations as the absolute and final answer to a problem and to think of changes in the raising of children in terms of definite "technics." It is often overlooked that a technic is only as effective as the spirit in which it is carried out.

It is at this point that the pediatrician's task becomes psychotherapeutic. He needs to appraise what type of a woman a mother is, what her attitude is in relation to the

child, how her personality problems enter into the picture, what she expects of him and how she will be able to carry out his recommendations. Without such an assessment of the individual mother there is the danger of giving recommendations which, though theoretically correct, will be unsuitable for a particular woman. It is a type of inquiry which can be carried out in pediatric practice. It involves less the taking a complete psychiatric history or delving deeply into the secrets of a mother's life than the ability to listen with alertness and attention to what the mother tells about herself when she reports her complaints about her child or about her own symptoms and ailments which she relates to the child.

A mother who is familiar with the ideas of modern psychology may be just as handicapped by inner conflicts and she may be just as rigid in using a so-called lenient method as an uninformed and old fashioned domineering mother.

The case of James may serve as an example. He was a healthy, well-developed infant of seven months but he kept his parents in a state of constant turmoil because he would not fall asleep. He was the only child of educated parents, both university graduates. He had slept well during the first four months of his life. Then the family moved to another town.

It was during these moving days that the child cried when put to bed. Both parents were enthusiasts about modern psychology and they were determined not to let their child suffer any frustration. The vicious circle began: whenever the child cried, either the father or mother would rush to his bed, pick him up and carry him around until he fell asleep. When put back to bed the child would wake up and cry again and the procedure was repeated. By the time the parents came for help it took several hours until he would fall asleep from sheer exhaustion. The effect was that he did not get enough sleep and also became fretful and irritable during the daytime—and both parents were near the breaking point.

Several experts had been consulted. A psychologist had recommended giving more demonstration of affection during the day-time because the child was "insecure." A pediatrician had advised the parents to leave the child alone even if he cried because they were encouraging a bad habit. The parents could not carry out his advice and felt that he was impatient and unsympathetic.

Though the advice was technically correct, the pediatrician had failed to consider the sources of tensions and uneasiness of these parents. They were so preoccupied with the task of "avoiding errors" and of saving the child from any suffering and frustration that they had sacrificed all their own comfort. Actually they had been very rigid and tense in handling the child and approached bedtime with real apprehension.

It was only after this basic interrelationship had been made clear to them, particularly that they were trying to avoid problems of their own lives, that they were able to be less anxious about the sleep problem and thus could permit the child to fall asleep. The unreasonable application of a sound educational principle had led in this case to a serious disturbance. Basically well meaning, these parents were nevertheless engaged in a noble competition dealing with who would be the better parent and, even more, in proving their superiority over their own parents, and probably also over the pediatrician.

Recognition of such conflicting attitudes on the part of parents in relation to a child may become the basis of effective psychotherapy. By helping a mother to become aware of her own personal conflicts she may be able to tend to the child's needs without letting her own problems interfere.

Observations of this type were made on mothers whose children suffered from diabetes and celiac disease. Some mothers seemed to be well able to carry out the necessary tasks of management, while others encountered great difficulties with correspondingly poor progress of the child. A large variety of individual problems were found to interfere with the success of treatment. To give just one example: the mother of a six-month-old girl who was doing amazingly well in spite of an operation for meconium ileus and volvulus on the first day of her life and of cystic fibrosis of the pancreas, became so anxious and upset at feeding time that she would have fainting attacks. When asked what was so difficult about the feeding, the mother made the astonishing statement that she was worried about what to tell the child when it grew up and could not have ice cream like her older sister. Many other remarks of this mother centered about the problem of jealousy and envy. This was such an outstanding theme that she could recognize it as a problem of her own life when her attention was drawn to it. A year later she was still amazed that her little girl did not envy her sister, but she had been able to bring up the child without letting her own problem of envy interfere with the child's development.

It is necessary, in such cases, to recognize some specific problem of the mother which interferes with her adequacy in handling the child. It should have some tangible relationship to her current living. Just to label her with a descriptive, symptomatic adjective —such as overprotective, domineering, rejecting, or over-anxious—is to dodge the problem of understanding.

In appraising a mother one needs to assess also her attitude toward the pediatrician. Medical practice is based on the assumption that people come to the doctor for diagnosis and advice. Patients differ enormously in their expectations of what a doctor will do for them. Modern psychiatry is much aware of the different ways in which patients relate themselves to their physician. The analysis and manipulation of the doctor-patient relationship is one of the specific tools of psychotherapy. In pediatrics the therapeutic possibilities of the appraisal of the doctor-patient relationship has not been dealt with systematically.

The way a mother approaches her physician gives clues as to what type of care she will be capable of carrying out, or in what way it should be given to her if there is no choice about the recommendation. A helpless child-like woman who looks up to her physician as to an all knowing father will be at a loss with a regime that leaves many decisions to her; she will be much too anxious to make valid observations on which to base her decisions. On the other hand a woman who has been active and independent all her life will resent being told every little detail. Since she cannot express this resentment towards her physician directly she might want to show what a good job she can do and be rigid and unspontaneous in her approach to the child—or disregard the doctor's advice altogether.

The different ways in which patients carry out recommendations and are able to cooperate seems to be closely allied to their personality and the relationship with their doctor. Patients who show poor cooperation, disregard advice or argue every point have been traditionally the object of medical scorn. If one approaches the ability to cooperate as an index of psychologic adjustment, it may become an entering wedge toward a better relationship.

Even good cooperation is not always a sign of healthy and normal attitudes. Quite

often over-obedient adherence to a regime is used as a weapon with which a mother keeps a child subdued. Unless special attention is paid to the punishing attitude of an overzealous mother and the psychologic damage to the child, harmful situations are apt to go unnoticed just because the mother cooperates so well.

I have stressed in my discussion the pediatrician's relationship to the mother. The younger a child the more exclusively it is possible to influence his emotional well being through influencing the mother.

My remarks cannot do more than hint at the psychotherapeutic possibilities through which the pediatrician in his role can play an important part in the promotion of better mental health. The purpose of this paper has been to draw attention to the psychiatric possibilities which are inherent in pediatric practice—as apart from the practice of psychiatry—and to stimulate systematic investigation of these factors.

SPANISH ABSTRACT

Aspectos Psicoterapéuticos de la Práctica Pediátrica

Se llama la atención a las posibilidades psicoterapéuticas inherentes a la práctica de la pediatría. Cada día se da uno más cuenta de la necesidad que existe de prestar mayor atención a los problemas sentimentales de la niñez, la que siempre ha ido acompañada de cierta inquietud con relación a los peligros y a las dificultades que la envuelven. Tales objeciones pueden justificarse si uno considera solamente las técnicas psicoterapéuticas especiales que se han desarrollado para el tratamiento de la neurosis y la psicosis como un acercamiento a los problemas psicológicos.

La relación entre el doctor y el paciente (en pediatría frecuentemente se encuentra la relación entre el doctor, la madre y el paciente) lleva en si posibilidades psicoterapéuticas, fundamentalmente las mismas que producen efecto en la situación psicoterapéutica más intrincada. La aplicación del conocimiento moderno psiquiátrico en la práctica pediátrica ha sido generalmente en la dirección de delinear métodos específicos para la crianza del niño, tal como el recomendar los alimentos cuando se piden espontaneamente en oposición a la alimentación metódica. Generalmente se han pasado por alto las posibilidades de utilizar individualmente la situación interpersonal. Este aspecto se ilustra con casos que demuestran el peligro de usar indistintamente la psicología "moderna" en el cuidado de infantes y niños y la necesidad de un acercamiento más individualizado. Otros ejemplos incluyen los problemas psicológicos del manejo médico de niños cronicamente enfermos e impedidos.

103 E. 84th St.

IMMUNOLOGIC AND BIOCHEMICAL STUDIES IN INFANTS AND CHILDREN, WITH SPECIAL REFERENCE TO RHEUMATIC FEVER

IV. Occurrence of Agglutinins in Normal and Abnormal Conditions

By PAUL F. DEGARA, M.D.
New York, N.Y.

LOW titers of agglutinative antibodies for Str. hemolyticus have been found in the sera of healthy man by Moser and von Pirquet.[1] Increase of titers may follow infections with Str. hemolyticus as well as other microorganisms (Tillett).[2] High agglutinin titers for special strains of Str. hemolyticus have also been detected by Cecil and deGara[3] in the majority of patients with rheumatoid arthritis. The presence of agglutinins for Str. hemolyticus does not necessarily indicate a preceding infection with these microorganisms. On the other hand, an increase in agglutinin titer would be expected unless the antibody forming system is impaired. It has been suggested by Coburn[4] that an inadequate immune response may be important in the mechanism of rheumatic fever. On the basis of this assumption, agglutinative antibodies should occur less frequently in members of families "susceptible" to the acquisition of rheumatic fever according to Wilson[5] and in known rheumatics than in non-rheumatic controls. A comparison of the degree of production of agglutinins for Str. hemolyticus in both normal and rheumatic individuals was therefore undertaken.

MATERIAL AND METHODS

I. *Sera:* A total of 497 sera from 372 children (171 males, 201 females) ranging in age from six months to 15 years were examined. These children were patients attending the Children's Clinic or the Cardiac Clinic, or hospitalized on the wards of New York Hospital. Most of the children had been under continuous medical supervision from birth as part of a genetic study. The sera were obtained in the usual manner and stored at 4° C. in paraffin sealed pyrex test tubes.

The following groups of children were studied:

A. Well children who had not been ill for at least one month preceding the test:
   1. 162 sera from 120 normal subjects.
   2. 56 sera from 40 rheumatic subjects.

B. Non-rheumatic children who were ill* at the time of the test or during the preceding month.

From the New York Hospital and the Department of Pediatrics, Cornell University Medical College.

Aided by a grant from The Commonwealth Fund.

(Received for publication June 8, 1948.)

* "Upper respiratory infections" include coryza, sinusitis, sore throat, pharyngitis and similar conditions, generally mild in origin and not accompanied by elevation of the body temperature.

"Infections presumably streptococcal in origin" include scarlet fever, tonsillitis, cervical adenitis, otitis media and similar conditions, generally accompanied by fever. Str. hemolyticus, beta, were cultured from most of the children in this group.

"Miscellaneous illnesses" include epidemic parotitis, pneumonia, nephritis, stomatitis, pseudohemophilia, infectious mononucleosis, hepatitis, rheumatoid arthritis and others.

1. 70 sera from 68 individuals with upper respiratory infections;
2. 39 sera from 28 individuals with infections presumably streptococcal in origin;
3. 52 sera from 43 individuals with miscellaneous illnesses.

C. Rheumatic children who had intercurrent illnesses at the time of the test or during the preceding month:

1. 24 sera from 23 individuals with upper respiratory infections;
2. 11 sera from seven individuals with infections presumably streptococcal in origin;
3. 12 sera from nine individuals with miscellaneous illnesses.

D. Children with active rheumatic fever:

1. 25 sera from 11 individuals who had a preceding infection presumably streptococcal in origin;
2. 46 sera from 23 individuals who had no history of a preceding infection.

II. *Antigens:* Three strains of Str. hemolyticus, beta, group A, were used.

1. Strain AB13 of Cecil, Nicholls and Stainsby[6] which is known to react with a majority of sera from patients with rheumatoid arthritis. This strain does not correspond to any known type; 2. Strain 23 RS84, a Type 14; and 3. Strain 11 RS50, a Type 26. Strains 2 and 3 were isolated and classified at the Rockefeller Institute for Medical Research and obtained through the courtesy of Dr. S. Rothbard who also kindly supplied specimens of absorbed type specific rabbit immune sera for control studies.

Stock cultures of the three strains were maintained in blood broth and passages made every four weeks. For the preparation of the suspensions to be used as antigens, subcultures were incubated for 18 hours at 37° C.

III. *Agglutination Reactions:* Details of the method have been described in a previous publication.[3]

In the present study only agglutinations in serum dilutions of 1 to 160 or more were designated as "Positive." Positive reactions were noted most frequently with strain AB 13 and somewhat less regularly with Type 14; no positive reactions were noted with Type 26. A patient was listed as having agglutinins for Str. hemolyticus if any serum examined during one illness reacted with either one or both strains of streptococci. Repeated positive results in the same patient were not counted when they occurred during the course of the same illness. The results obtained are presented in Table I.

Results

Relation of Streptococcal Agglutinins to Susceptibility to Rheumatic Fever:[5] It will be seen from Table I that streptococcal agglutinins were found in 8.7% of 160 well children examined. There was no difference between the incidence of agglutinins for Str. hemolyticus in 120 non-rheumatic and 40 rheumatic subjects. Similarly, a comparison of the occurrence of streptococcal agglutinins during or following various intercurrent illnesses shows that there is no essential difference between normal and rheumatic individuals.

Further evidence for the statement that there were no differences between rheumatic and normal children was obtained from a comparison of siblings from "susceptible" and "insusceptible" families in health and during illness. The agglutinin titers of 62 siblings from 26 "susceptible" families were compared with those of 68 siblings from

TABLE I

PRESENCE OF AGGLUTININS FOR STR. HEMOLYTICUS IN SERA FROM NORMAL AND RHEUMATIC CHILDREN IN HEALTH AND DURING ILLNESS

Group	Illness	Persons Examined	Agglutinins Present	
			No.	%
Normal	None	120	11	9.2
Rheumatic (Inactive)	None	40	3	7.5
Total Well		160	14	8.7
Normal	Upper Respiratory Infections	68	5	7.3
	"Streptococcal" Infections	28	11	38.6
	Miscellaneous	43	3	6.9
Rheumatic (Inactive)	Upper Respiratory Infections	23	2	8.7
	"Streptococcal" Infections	7	5	71.4
	Miscellaneous	9	1	11.1
Total	Upper Respiratory Infections	91	7	7.7
	"Streptococcal" Infections	35	16	45.7
	Miscellaneous	52	4	7.7
Rheumatic (Active)	With Antecedent "Streptococcal" Infections	11	9	81.8
	Without Antecedent Infections	23	3	13.0
Total Active Rheumatic		34	12	35.2
Total Ill		212	39	18.4

30 "insusceptible" families. No differences were noted in the incidence of high agglutinin titers in the two groups.

Relation of Streptococcal Agglutinins to Various Illnesses: The data presented in Table I indicate that a significantly greater number of high agglutinin titers were found in the group of children who had experienced infections, presumably streptococcal in origin. The occurrence of these antibodies during or following mild upper respiratory infections or miscellaneous diseases was approximately the same as that of a group of well children.

Relation of Streptococcal Agglutinins to Active Rheumatic Fever: It is apparent from Table I that agglutinins for Str. hemolyticus occur approximately to the same degree in children with active rheumatic fever who did not experience antecedent infection and in normal children. The group of children with "Active rheumatic fever and preceding 'streptococcal' infection" showed a significantly greater number of agglutinins for Str. hemolyticus.

COMMENT

No evidence was obtained to indicate that rheumatic individuals differ in their immune response from normal subjects with respect to the production of agglutinins

for Str. hemolyticus. In a previous publication[7] the incidence of agglutinative antibodies for H. pertussis following either immunization or natural exposure to the disease was studied in the same group of children. The results were identical for rheumatic and non-rheumatic subjects. Wilson[8] made similar observations on Schick tests following immunization in the same group of children.

In children with active rheumatic fever, agglutinins for Str. hemolyticus were found in high titer in nine out of 11 cases in which an infection, presumably streptococcal in origin, had preceded the rheumatic episode. Without such an antecedent infection, however, only three out of 23 children had high titer for streptococcal agglutinins, an incidence which is comparable to that of non-rheumatic subjects. This would indicate the majority of our patients with active rheumatic fever presented no clinical or immunologic evidence for a preceding streptococcal infection.

It is also noteworthy that there was a correlation between the agglutinin titers and the amount of gamma globulin present in the serum as determined by electrophoresis (Wilson, et al.);[9] however, in serial determinations it was found that agglutinin titers showed a more rapid decrease to normal values than the gamma globulin.

Summary

Agglutinative antibodies for three different strains Str. hemolyticus, beta, group A, were studied in 497 sera from 372 children. A high titer was found in approximately 9% of well children.

There was no significant difference between rheumatic and non-rheumatic subjects in the incidence of high agglutinin titers for Str. hemolyticus.

Following infections, presumably streptococcal in origin, approximately 46% of the children examined had high agglutinin titers for Str. hemolyticus.

In active rheumatic fever, agglutinins were present in high titers in nine out of 11 patients who had experienced an antecedent illness, presumably streptococcal in origin. Of 23 patients with no history of such an infection, only three had streptococcal agglutinins.

Conclusion

No evidence was obtained to indicate that the immune response of "susceptible" and rheumatic children to infections, presumably streptococcal in origin, is different from that of non-rheumatic subjects.

References

1. Moser, P., and von Pirquet, C., Zur Agglutination der Streptokokken, Zentralbl. Bakter. I. O. **34**:560, 1903.
2. Tillett, W. S., and Abernethy, T. J., Serological reactions with hemolytic streptococci in acute bacterial infections, Bull. Johns Hopkins Hosp. **50**:270, 1932.
3. Cecil, R. L., and deGara, P. F., Agglutination reaction for hemolytic streptococci in rheumatoid arthritis; its significance in diagnosis and treatment, Am. J. M. Sc. **211**:472, 1946.
4. Coburn, A. F., Rheumatic fever problem; present status, Am. J. Dis. Child. **70**:339, 1945.
5. Wilson, May G., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. I. Role of genetic susceptibility, Pediatrics **2**:239, 1948.
6. Cecil, R. L., Nicholls, E. E., and Stainsby, W. J., Etiology of rheumatoid arthritis, Am. J. M. Sc. **181**:12, 1931.
7. deGara, P. F., and Mayer, S. A., Agglutinative reaction for hemophilus pertussis following whooping cough and following immunization, J. Pediat. **30**:171, 1947.
8. Wilson, May G., Unpublished observations.

9. Wilson, May G., and Lubschez, R., Immunologic and biochemical studies in infants and children with special reference to rheumatic fever. VI. Electrophoretic patterns of blood plasma and serum in rheumatic fever. To be published.

SPANISH ABSTRACT

Estudios Inmunológicos y Bioquímicos en Infantes y Niños con Referencia Especial a la Fiebre Reumática. IV. Aparición de Aglutininas en Condiciones Normales y Anormales

Se estudiaron las aglutininas para tres cepas de estreptococos Grupo A beta hemolítico en 497 sueros de 372 niños. En los análisis se encontró un titulo alto en aproximadamente 46% de los niños que habían tenido infecciones presumiblemente de origen estreptocócico. En la fiebre reumática activa se encontraron presentes altos titulos en nueve de cada 11 pacientes que habían tenido anteriormente infección presumiblemente de origen estreptocócico. De los 23 pacientes reumáticos que carecían de datos de enfermedad precedente, solamente tres nostraron concentraciones de aglutininas estreptocócicas.

525 E. 68th St.

INFECTIOUS CROUP. II. "VIRUS" CROUP

By EDWARD F. RABE, M.D.
New Haven, Conn.

IN A PREVIOUS publication,[1] infectious croup was defined and the clinical variations in the extent of this disease (laryngitis, laryngotracheitis, laryngotracheopneumonitis) were described. It was shown that as a result of studying the bacteriology, pathology, and clinical course of 347 cases of infectious croup the patients could be grouped in three etiologic categories; namely, diphtheritic croup, H. influenzae type B croup, and so-called "virus" croup.* In this paper the pathology, clinical course, and treatment of 297 cases of so-called "virus" croup will be discussed in detail. Concurrently it will be shown how this form of infectious croup differs from those due to bacteria.

MATERIALS AND METHODS

All of the 347 patients with infectious croup were admitted to the Pediatric Service of the New Haven Hospital during the ten year period 1937-1946, inclusive. Data were derived from the clinical records of these patients which included observations by members of the Otorhinolaryngological Staff. Protocols of autopsied cases were obtained for study from the Department of Pathology, Yale University School of Medicine. Additional information on fatal cases was obtained from filed microscopic sections and gross material which was furnished by the Department of Pathology.

LIVING PATHOLOGY

The endoscopic picture of "virus" croup is affected by the degree of downward spread of the infection, the duration of infection, and the virulence of the disease. Early in the illness the mucosa of the pharynx, larynx, and usually the trachea is moderately injected, red, and edematous. Supraglottic edema is rarely if ever extreme. When it is present it involves predominately the ventricle and aryepiglottic folds. However, the swelling in the loose subglottic tissue is often marked and accounts for the early obstructive symptoms. This is especially true in young infants because in them there is relatively more loose subglottic connective tissue than in older children (Brennemann et al).[2] Early in "virus" croup there is much secretion found in the larynx and trachea. The secretion is first thin, but as the duration of the infection lengthens the secretion becomes thick and tenacious. With downward spread of the disease and the production of laryngotracheopneumonitis, the lower respiratory tract is occasionally covered by a grey-yellow, fibrinous or even glazed crust. When secretions are tenacious or crusting occurs obstruction of the bronchi can be observed.

There was no correlation between the various bacteria recovered from the respiratory tract and the appearance of crusting. Nor was crusting an invariable sequel of tracheotomy. Instead, crusting of the mucosa of the airway was apparently related to the duration and/or virulence of the infection.

Department of Pediatrics, Yale University School of Medicine and the University Service, Grace-New Haven Community Hospital.

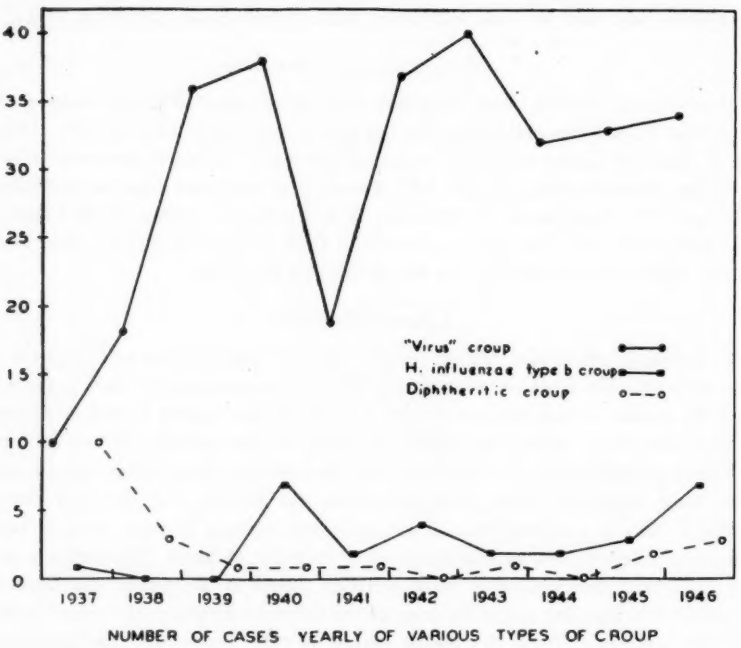
(Received for publication April 1, 1948.)

* For a discussion of the propriety of this term see the first paper in this series.

Valuable aid in the preliminary differentiation of the etiologic types of infectious croup can be secured with the endoscope. Marked epiglottitis with severe supraglottic injection and edema is indicative of H. influenzae type B croup,[3,4] while membranous pharyngitis, laryngitis, and tracheitis is supportive evidence of Klebs-Löffler b. infection (Jackson).[5] Mild supraglottic and moderate to marked subglottic edema, or edema involving principally the region of the true cords and ventricle, is indicative of so-called "virus" croup. However, the final diagnosis always rests with adequate bacteriologic investigation of each case.

Morbid Pathology

Five of the eight fatal cases of so-called "virus" croup were examined postmortem. All autopsied patients were, clinically, cases of laryngotracheopneumonitis.



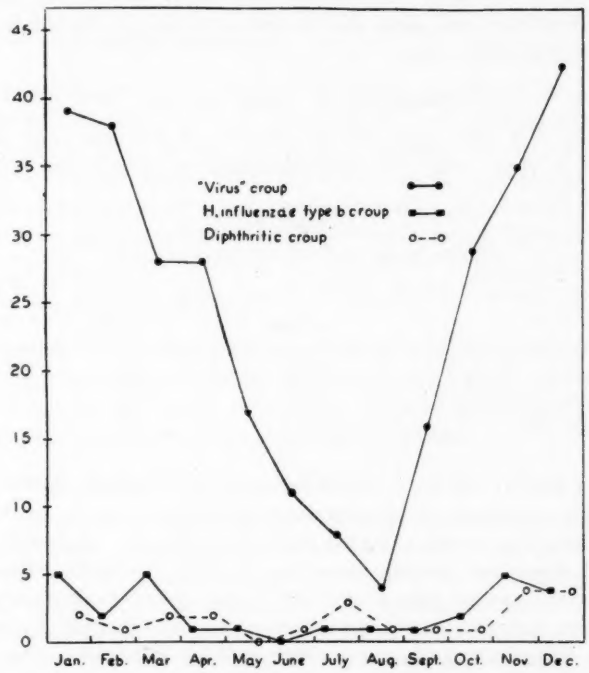
NUMBER OF CASES YEARLY OF VARIOUS TYPES OF CROUP

Chart I

The gross pathologic picture of so-called "virus" croup was characterized by edema of the respiratory tract which was most marked in the subglottic region. The airway from the larynx to the bronchi contained a mucoid exudate and the lining epithelium was spottily covered by a fibrinous membrane. Microscopically this membrane was composed of necrotic debris, fibrin, mucus, and a mixture of round cells and polynuclear leukocytes. Microscopic examination of the larynx, trachea, and bronchi showed a primary spotty surface ulceration with congestion and edema of the submucosa. The mucous glands showed variable degrees of toxic degeneration, from one area to another. In cases ill longest (e.g. nine days) there was extensive glandular degeneration in all sections exam-

ined. In areas where such degeneration was severe, a fibrinous membrane was noted on the adjacent mucosa. In the lung the bronchiolar mucosa, and in some areas, the bronchiolar walls, were often destroyed and the lumina were plugged with polynuclear leukocytes and fibrin. A surrounding bronchopneumonia, atelectasis and alveolar emphysema were common. Microscopic evidence suggestive of pulmonary interstitial emphysema was usually found but in only one instance was this extensive.

Attempts to correlate this consistent pathologic picture with the recovery of the same potential pathogen from each case were fruitless. Of the five autopsied cases four had blood cultures performed. None of the cultures was positive.



NUMBER OF CASES MONTHLY OF VARIOUS TYPES OF CROUP

CHART II

This pathologic picture has a pronounced similarity to laryngotracheitis in chickens. In a series of papers Beach and Seifried[6,7,8] and later Burnet and Foley[9] demonstrated conclusively the virus etiology of the disease. A striking similarity exists also between the pathology of so-called "virus" croup and the pathology of viral influenza[10] in man as described by Winternitz et al.[11]

The principal difference between the pathology of "virus" croup and croup due to bacteria is to be found in the consistent absence in "virus" croup of certain pathologic features of H. influenzae type B croup and diphtheritic croup. The occurrence of the

following pathologic findings in croup due to H. influenzae type B and their absence in "virus" croup defines the main pathologic difference between these two types of croup: first, the very frequent occurrence of marked to extreme supraglottic edema with epiglottitis, second, severe degeneration of the mucous glands of the laryngotracheobronchial tree early in the disease and third, the occurrence of mucosal ulcerations secondary to submucosal abscesses, which abscesses appear very early in the course of the infection.[4] Diphtheritic croup differs pathologically from "virus" croup because of the consistent appearance of the following changes in diphtheritic croup: first, early formation of a thick, gray, adherent membrane which often begins in the pharynx and spreads downward into the respiratory tract; second, early degeneration of the mucous glands of the respiratory tract, and third, the frequent occurrence of pathologic changes in sites outside the respiratory tract.[12]

Incidence of "Virus" Croup

Eighty-six per cent (297 cases) of the 347 cases of infectious croup in this series were classified as "virus" croup. The yearly admissions for "virus" croup varied as shown

TABLE I

Age Incidence of Etiologic Types of Croup

Type	Distribution among age groups		
	0–3 years	3–7 years	7–13 years
"Virus" croup	61%	32%	7%
H. influenzae type B croup	21%	65%	14%
Diphtheritic croup	32%	55%	13%

in Chart I, but bore no relation to the incidence of other etiologic types of croup. The highest monthly admissions for this disease occurred from October to the following April (Chart II). This period accounted for 81% of the total admissions for the disease. Chart II shows that monthly admissions for croup due to H. influenzae type B tend to follow the seasonal pattern of "virus" croup; whereas, diphtheritic croup admissions occurred with similar frequency during any season of the year. The age incidence of the various etiologic types of croup is shown in Table I. It is interesting to note that "virus" croup is predominately a disease of children under three years of age; whereas, both bacterial types of croup occur most frequently in the age group three to seven years of age.

There was a definite predilection for male children in "virus" croup, for 70% occurred in this sex. There were 220 individuals represented by these 297 cases. Eighty-two individuals (37%) had had croup more than once. Twenty-eight of these patients (13%) were admitted to the hospital because of croup two or more times. Two patients were admitted six times, one seven times, and one ten times. As these children grew older they were admitted less frequently; finally, with each upper respiratory tract infection they were hoarse without having respiratory obstruction in addition. Fifteen per cent of the children had a family history of croup. It appears possible that children with repeated attacks of croup have an anatomically inferior larynx as compared with the normal population, and that this predisposition is inherited.

TABLE II

YEARLY INCIDENCE AND MORTALITY OF CLINICAL TYPES OF "VIRUS" CROUP

	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	Totals
Laryngitis	5	10	23	15	13	23	9 (1)	17	24	22	161
Laryngotracheitis	5	5	6	16	5	8 (1)	24	13	5	11	98
Laryngotracheo-pneumonitis	0	3	7 (1)	7 (2)	1	6	7 (2)	2	4 (1)	1	38
Total	10	18	36 (1)	38 (2)	19	37 (1)	40 (3)	32	33 (1)	34	297

Note: Fatal cases are included in parentheses.

That this disease might have its basis in an allergic constitution is an observation not borne out by the study. Sixty-four (29%) of the 220 individuals had a family history of a minor or major allergy. Twenty-two (10.0%) of these patients had had obvious allergies (eczema, asthma, hives, urticaria). Five per cent of the cases showed an eosinophilia (over 3%). In a few instances adrenalin chloride (0.2 cc., 1/1000 dilution) was given subcutaneously but no benefit was apparent. Inasmuch as the incidence of allergy in the general population is approximately 10%[13] and 75% of persons with allergies have a positive family history for the disease,[14] allergy per se seems to play little part in the etiology of "virus" croup.

A yearly variation in the severity of "virus" croup was noted (Table II). Generally speaking, in the years with the highest incidence of the disease, there was a larger number of the more severe clinical types of the infection (laryngotracheitis, laryngotracheopneumonitis) with a correspondingly higher mortality.

SIGNS, SYMPTOMS AND EARLY COURSE OF "VIRUS" CROUP

All of the patients gave a history of an antecedent upper respiratory tract infection which varied in duration from one day to three weeks before croup appeared. Respiratory stridor with or without hoarseness usually appeared first at night, and was often sudden in onset. In cases seen in the hospital, this symptom had progressed despite the common remedies used in the disease, i.e., induced emesis, steam inhalations, and sulfonamides by mouth. The average duration of symptoms of partial respiratory obstruction before hospitalization was 1.2 days.

On admission the children showed signs of upper respiratory tract infection and vary-

TABLE III

COMPARISON OF COURSE OF CLINICAL TYPES OF "VIRUS" CROUP

	Duration of hospital stay-average number of days (Surviving patients)	Mortality %	Number of cases
Laryngitis	6.6	0.6	161
Laryngotracheitis	9.1	1.0	98
Laryngotracheopneumonitis	16.7	15.8	38

ing degrees of respiratory tract obstruction. Signs of severe toxicity as described in H. influenzae type B croup[3,4] were lacking in this group save for a few patients who had been ill with severe respiratory tract obstruction for one or two days. It was these children who were moderately cyanotic, restless, and tired, and whose clinical appearance seemed in proportion to the duration of partial anoxia.

By evaluating the admission physical findings and the subsequent clinical course of these 297 patients the extent of their disease was divided into three clinical groups as previously defined.[1] Table III shows that as the disease progressed downward in the respiratory tract the length of the hospital stay and the mortality increased. There was no correlation between admission total white or differential blood cell counts and any of the following: clinical type of croup, length of hospitalization, incidence of tracheotomy, or mortality. The temperature on admission varied from 37° to 40° C. If the clinical condition was severe (due to partial anoxia), the admission temperature tended to be higher, but this was not invariably true.

Treatment

Following admission, all patients were placed in a steam room. An immediate consultation by the Otorhinolaryngological Service was requested. The individual patient was then watched carefully to determine whether or not operative interference was indicated. If improvement was not noticed and if the child was restless, showed marked retraction, and exhibited poor respiratory exchange by repeated auscultation, tracheotomy was performed. Once the child's condition seemed certain to the observer, and when operation was not indicated, special attention was given to disturbing the child as little as possible. If the patient was not retracting severely, and at the same time was extremely excited, sedation with rectal seconal was instituted.

Laryngoscopy was performed on only 11% of the patients. When the clinical condition on admission as determined by history and physical findings seemed clear-cut, this procedure was not performed. However, if unallayed suspicion existed regarding the presence of diphtheria or H. influenzae type B croup, laryngoscopy was performed as a source of additional information in attempting to determine the etiologic type of infectious croup.

Sulfonamides have been used in our clinic in the treatment of "virus" croup since 1940. From a detailed review of all cases it was concluded that sulfonamides were of no proven value in the mild or moderate forms of "virus" croup and that they had no effect upon the tendency to form crusts in the respiratory tract. However, it has been our practice to give sulfonamides to severely ill patients with "virus" croup in the hope of combating the rare bacteremia or occasional pneumonia which occurs during the course of the infection. Whether this was actually accomplished could not be evaluated from our figures. At present, sulfadiazine is always given to every croup patient until cultures assure the absence of H. influenzae type B from the rhinopharynx and blood. As a preventive measure sulfadiazine or penicillin is given to any croup patient harboring potential pathogens in the rhinopharynx.

Maintenance of fluid balance was given particular attention in all cases. If the child was anemic or severely ill with laryngotracheopneumonitis, or if the course of convalescence was unusually prolonged, transfusions of whole blood were given.

Simple laryngeal suction was applied to only one case. This was done on two occasions

and the child was then tracheotomized. Intubation was not performed on any case in this group. The main reasons for avoiding this procedure have been the necessity for constant, trained supervision to replace coughed-up tubes, and fear of laryngeal stenosis as a complication of intubation.

Complications in Non-tracheotomized Patients

The incidence of complications in the 262 non-tracheotomized patients was 13%. These consisted of lobar pneumonia, bronchopneumonia, and otitis media (Table IV). Pneumococci were etiologically implicated in four cases while convincing implication of Str. hemolyticus and H. influenzae was not encountered. From these observations it

TABLE IV

Complications in Non-Tracheotomized Patients (262)

Complication	Number of cases	Remarks
1. Pneumonitis (lobar by X-ray)	5	Pneumococcus recovered (2 cases)
2. Bronchopneumonia (X-ray)	3	Pneumococcus recovered (2 cases)
3. Otitis media, purulent, bulging MT	7	Aural discharge, 1 case (drained previous month)
4. Otitis media, catarrhal	18	Post measles, 2 cases
5. Drug reaction	1	Sulfadiazine hematuria

appears that bacteria account infrequently for complications in the course of non-tracheotomized "virus" croup.

One non-tracheotomized patient died. The child expired shortly after a temperature rise to 41° C. The cause of the death was never adequately explained. Thus, in the absence of severe respiratory tract obstruction "virus" croup is a disease of few complications and the over-all prognosis is good.

Analysis of Tracheotomized Patients

Thirty-five cases of "virus" croup were tracheotomized, an incidence of 12%. Tracheotomy was performed on a very young age group, the average age of these children being 19 months. The necessity for tracheotomy could not be correlated with the duration of the preceding upper respiratory infection, the duration of croup before hospitalization, the admission temperature, or the total leukocyte and differential white blood cell count. Among these 35 patients there were one case of laryngitis, 16 cases of laryngotracheitis, and 18 cases of laryngotracheopneumonitis. The only unusual physical finding presented by these cases on admission, other than signs of severe respiratory obstruction, was an exudative pharyngitis which was noted in two instances. One of these cases was endoscoped and a non-membranous laryngitis was observed.

Eighteen of these patients were laryngoscoped on admission. It is noteworthy that marked epiglottic edema, as seen in H. influenzae type B coup, was not described. Seven of the cases showed subglottic swelling—three exhibited edema of the true

cords and ventricle, and eight patients had mild to moderate supraglottic swelling involving either the false cords or the aryepiglottic folds.

Tracheotomy was performed from ½ hour to 30 hours after admission to the hospital (average, six hours). There were two exceptions: one patient was tracheotomized three days, the other, five days after admission. Both were subsequently shown to have mediastinal emphysema and pneumothorax. All operations were performed by the Otorhinolaryngological staff.

Following tracheotomy patients were kept in steam until at least two days after successful decannulation. During this period frequent intracannular instillations of saline followed by suction with a small catheter were found to give symptomatic benefit. A few

TABLE V

SUMMARY OF CLINICAL COURSE OF TRACHEOTOMIZED PATIENTS WITH INFECTIOUS CROUP ACCORDING TO ETIOLOGIC TYPE

	"Virus" croup	H. influenzae type B croup	Diphtheritic croup
Number of cases	35	13	9
Percent of total tracheotomized	11.8%	48.0%	45.1%
Average age	19 mo.	40 mo.	34 mo.
Range of age	6 mo. to 54 mo.	4 mo. to 84 mo.	4 mo. to 84 mo.
Duration of antecedent illness (URI)-average	4.2 days	2.7 days	4.5 days
Duration of croup before hospitalization-average	1.9 days	8.6 hours	1.9 days
Admission temperature—average	39.0° C.	39.0° C.	38.2° C.
Admission leukocyte count—average			
total	13,200	24,300	16,600
polynuclear	63%	85%	75%
lymphocytes	34%	13%	22%
Duration of cannulation—average	14.8 days	6.8 days	12.2 days
Duration of hospital stay, surviving patients—average	25 days	13 days	31 days
Incidence of positive blood cultures	2.9% (1)	92.3% (12)	33.3% (3)
Type of bacteria in blood culture	Pn XIX	H inf. type B	l. C. diphtheriae (P.M.*) Pn XIX l. C. diphtheriae (P.M.) Pn IX l. C. diphtheriae (P.M.)
Mortality	20.0%	15.4%	44.5%

* Postmortem.

patients with severe respiratory obstruction despite tracheotomy were maintained in an oxygen tent. The average duration of cannulation was 15 days and the average length of hospitalization in the surviving patients was 25 days. Seven of the tracheotomized patients died, a mortality of 20%.

Table V presents a summary of the clinical course of tracheotomized patients with infectious croup according to the etiologic type of the disease. It is to be noted that the course of both "virus" croup and diphtheritic croup is a slow one in comparison with that of H. influenzae type B croup. The table also emphasizes the difference in age incidence between the bacterial and non-bacterial forms of the disease. The difference in the post-tracheotomy course of H. influenzae type B croup and the other two forms of the disease is marked. In the former type difficulty with excessive mucus from the tube and prolonged periods of cannulation are rare while these difficulties are commonplace in "virus" and diphtheritic croup.

Complications occurred in the course of 80% of the tracheotomized cases. The most serious complication, and a not infrequent one, was crusting of the secretions in the

bronchial tree. There were six such patients, three of whom died. Of the three surviving patients with this complication two were bronchoscoped 20 times within a two week period for removal of crusts and the third child was bronchoscoped twice within a week's time. The three fatal cases developed mediastinal emphysema and pneumothorax in addition to crusting of the airway.

Baum[15] has long contended that crusting of the bronchial secretions was "man made" and resulted from the drying effect of air passing into the trachea without the warming and moistening that results from natural passage through the nose. This explanation does not appear to satisfy all the observed facts in this series. One of the children with severe croup was bronchoscoped prior to tracheotomy. Some isolated areas of crusting were already present in the laryngotracheal airway. Eighteen other tracheotomized and endoscoped patients who survived were cannulated for an average period of 14 days and in these crusting did not occur. It is our impression that this complication follows as the result of a temporary cessation of function of the mucous secreting glands of the respiratory tract (part of the pathologic physiology of the disease) with a consequent drying and crusting of the previous secretions and the necrotic debris which is present.

The most common complication, and of equally serious import as the first described, was the development of mediastinal emphysema and/or pneumothorax. Such an event occurred in 30% of the tracheotomized cases. The mechanism of production of this complication, and the seriousness of the sequelae have been adequately reviewed in recent literature[16,17] and need no detailed discussion here. It will be sufficient to say that there are two probable routes of producing the complication: the intrinsic route, in which there occurs minute perivascular alveolar ruptures in the lung leading to pulmonary interstitial emphysema, which in turn leads to mediastinal emphysema, pneumothorax, pneumoperitoneum and subcutaneous emphysema; and the extrinsic route, in which air enters the superior mediastinum behind the pretracheal fascia when skeletization of the trachea for tracheotomy is performed. Once air has entered the superior mediastinum it can extend into contiguous anatomic areas. From our observations it is apparent that the operation of both mechanisms leads to the production of mediastinal emphysema and pneumothorax in "virus" croup.

The intrinsic route was apparently responsible for the production of pneumothorax in one child and mediastinal emphysema and pneumothorax in another. In the first instance a two-year-old child was ill at home with severe laryngitis for three days. On admission and prior to tracheotomy X-ray examination revealed bilateral pneumothorax. (The possibility that this child had mediastinal emphysema is not ruled out by "negative" X-ray.)[18] The second child, age 3½ years, was ill with croup for three days. She was watched in the hospital steam room for 36 hours, at the end of which time she suddenly became cyanotic, had distant breath sounds over the upper chest and yet had no obvious increase in respiratory stridor. Upon skeletization of the trachea there was a bulge of the fascia about the trachea, a peritracheal emphysema. Following tracheotomy respiratory relief was marked. Immediate post-tracheotomy chest X-ray showed moderate mediastinal emphysema, a small left pneumothorax and slight subcutaneous emphysema.

Of the remaining nine cases with mediastinal emphysema or pneumothorax no data were available to determine whether or not the complications existed prior to tracheotomy. They were diagnosed following tracheotomy. According to Forbes, et al,[17] the most likely path for the air to enter the mediastinum in such cases would be the extrinsic

route. However, in four of these cases either tenacious mucus or crusting caused fatal respiratory tract obstruction. In these instances it is possible that pulmonary interstitial emphysema (air traveling the intrinsic route) could initiate or propagate mediastinal emphysema and pneumothorax.

Table VI enumerates the complications found in the 35 tracheotomized cases. The incidence of atelectasis is low when one considers the pathology of the disease and the

TABLE VI

COMPLICATIONS IN TRACHEOTOMIZED PATIENTS (35)

Complication	Number of cases	Remarks
1. Crusting of tracheobronchial secretions	6	Mortality—50.0%
2. Mediastinal emphysema and/or pneumothorax (proved by X-ray in 9 cases, P. M.* 1, 1 with subcutaneous emphysema)	11	Mortality—45.3%
3. Pneumonia (X-ray diagnosis)		
a. bronchopneumonia	7	Recovered Pn. from 5, only 2 typable
b. lobar	3	Pn. from all cases, i.e. Pn V, Pn XVIII, Pn XIX and Pn XXII
4. Atelectasis (X-ray diagnosis)	4	3 patients had severe crusting of airway
5. Septicemia (Pn. XIX)	1	Treatment with sulfapyridine. Recovered
6. Bronchiectasis	1	Bronchoscoped 19 times in 13 days for removal of crusts. Followed for 2 years. Diagnosis by X-ray (RLL)
7. Serum reaction (diphtheria antitoxin)	1	
8. Drug reaction (sulfadiazine)	3	

* Postmortem.

number of cases with obvious crusting of the airway. The discrepancy may be partially explained by the fact that not all cases were examined roentgenologically.

ANALYSIS OF DEATHS

In the total series the mortality was 2.7%. However, only one fatality occurred in each of the clinical groups defined as laryngitis and laryngotracheitis, producing a mortality of 0.6% and 1.0% respectively. There were six deaths among the cases of laryngotracheopneumonitis, a mortality of 16% for this form of the disease. In only one fatal case was respiratory embarrassment not an obvious contributing cause of death. This case of laryngitis has been discussed previously.

In each of the remaining seven fatal cases evidence of severe respiratory tract obstruction and consequent extra-alveolar thoracic air was obtained. All of these cases were

tracheotomized. The obstruction was due mainly to crusting in three cases, to thick tenacious exudate in three cases, and to edema of the larynx and trachea in the other case. Five of the cases had mediastinal emphysema with extension of air into contiguous areas in three cases. The sixth case had severe hilar interstitial emphysema, and the seventh had only microscopic interstitial emphysema plus extensive atelectasis and alveolar emphysema. Bacteremia was not present in any of the seven fatal cases which were cultured. Significant pathologic changes were not found in other parts of the body. It is, therefore, apparent that the most important cause of death in "virus" croup is respiratory tract obstruction with ensuing respiratory embarrassment.

Discussion

This study has shown that the most serious and frequent complication in "virus" croup is some form of extra-alveolar thoracic air. The finding is in agreement with other reports.[17,19] Since in this series 45% of the cases so affected died, it is imperative to review methods for the prevention and treatment of this complication.

Mediastinal emphysema and pneumothorax can occur in so-called "virus" croup before as well as following tracheotomy. More often these complications are apparent following operation. Two measures are available for minimizing their chances of occurrence. The first is early tracheotomy, i.e., not waiting until the child is either cyanotic or moribund but operating when restlessness increases and poor respiratory exchange is consistently evident by auscultation. As shown in this study crusting of the airway is not a complication of the operation per se, so that such a consideration should never delay tracheotomy. The second measure consists in pretracheotomy laryngotracheal decompression by the insertion of a bronchoscope through the glottic chink. Convincing statistical data concerning the effectiveness of this procedure in lowering the incidence of post-tracheotomy mediastinal emphysema and pneumothorax have been recently published.[17] When mediastinal emphysema and pneumothorax have developed to an extent which causes respiratory embarrassment, periodic or continuous needle aspiration of the air is the treatment of choice.

The frequency of occurrence of pulmonary interstitial emphysema among these cases is difficult to ascertain. It is reasonable to assume that it occurs often in association with other forms of extra-alveolar thoracic air, especially in those cases in which mediastinal emphysema and pneumothorax develop before tracheotomy.[16] Once developed pulmonary interstitial emphysema frequently persists in spite of gross methods to alleviate it, and when generalized, its effects are serious.[16] In such a situation inhalations of moist oxygen or a mixture of moist oxygen and helium would be anticipated to give the patient relief and hasten resolution of the pulmonary interstitial emphysema. Oxygen will be absorbed by any area supplied by capillaries while helium can diffuse through tissues into the air.[20] The behavior of these gases is in contrast to nitrogen (the usual inert vehicle for oxygen) which apparently perpetuates pulmonary interstitial emphysema because of its slow absorption and poor diffusability from extra-alveolar sites, and its large tissue fat solubility. If short periods of inhalation (under 12 hours) are to be used, 100% oxygen is satisfactory. However, if prolonged inhalation therapy (over 12 hours) is necessary the oxygen concentration should not exceed 60%. Higher concentrations produce damage to the lung and a reduction of the vital capacity.[21,22] It should be kept in mind that a humidifying system must be used in all types of oxygen administration.[23]

Summary

Of the three etiologic types of infectious croup the most frequently occurring type in this study was so-called "virus" croup.

The pathology of so-called "virus" croup is distinct from that of croup due to H. influenzae type B and C. diphtheriae. It is similar to viral influenza in man and viral laryngotracheitis in chickens.

Clinically "virus" croup is a progressive disease with downward spread of the infection in the respiratory tract. The inflammation can extend to various regions resulting in the clinical forms of the disease known as laryngitis, laryngotracheitis, or laryngotracheopneumonitis. The mortality increases as the disease spreads down the respiratory tract.

There is no well-founded specific treatment for "virus" croup. However, sulfadiazine should be given to all infectious croup patients until cultures of the rhinopharynx and blood assure the absence of H. influenzae type B. Continued chemotherapy should be given all patients severely ill with the disease.

The most frequent and severe complication of "virus" croup is some form of extra-alveolar thoracic air. The most common cause of death is respiratory embarrassment.

Acknowledgements

The author wishes to acknowledge the valuable advice and criticism given him in the preparation of this paper by Dr. Grover F. Powers, Dr. Paul L. Boisvert, and Dr. Donal L. Dunphy.

References

1. Rabe, E. F., Infectious croup. I. Etiology, Pediatrics **2**:255, 1948.
2. Brennemann, J., Clifton W. M., Frank, A., and Holinger, P., Acute laryngotracheobronchitis, Am. J. Dis. Child. **55**:667, 1938.
3. Sinclair, S. E., H. influenzæ type B in acute laryngitis with bacteremia, J.A.M.A. **117**:170, 1941.
4. Rabe, E. F., Infectious croup. III. H. influenzæ type B croup. To be published.
5. Jackson, C., and Jackson, C. L., Acute laryngotracheobronchitis, J.A.M.A. **107**:929, 1936.
6. Beach, J. R., Bacteriological study of infectious laryngotracheitis of chickens, J. Exper. Med. **54**:801, 1931.
7. Beach, J. R., Filterable virus, cause of infectious laryngotracheitis in chickens, J. Exper. Med. **54**:809, 1931.
8. Seifried, O., Histopathology of infectious laryngotracheitis in chickens, J. Exper. Med. **54**:817, 1931.
9. Burnet, F. M., and Foley, M., Infections of respiratory tract of chick embryos by viruses of psittocosis and infectious laryngotracheitis. Comparison with influenza virus infections, Australian J. Exper. Biol. & M. Sc. **19**:235, 1941.
10. Smith, W., Andrewes, C. H., and Laidlaw, P. P., Virus obtained from influenza patients, Lancet **2**:66, 1933.
11. Winternitz, M. C., Wason, I. M., and McNamara, F. P., Pathology of influenza, Yale University Press, New Haven, 1920, p. 13-31.
12. Councilman, W. T., Mallory, F. B., and Pearce, R. M., Study of bacteriology and pathology of 220 fatal cases of diphtheria, J. Boston Soc. Med. Scien. **5**:137, 1900.
13. Cooke, R. A., Allergy in Theory and Practice, W. B. Saunders Co., Philadelphia, 1947, p. 10.
14. Rubin, M. I., In Mitchell-Nelson, Textbook of Pediatrics, W. B. Saunders Co., Philadelphia, 1946, p. 1234.
15. Baum, H. L., Treatment of acute laryngotracheobronchitis, Arch. Otolaryng. **41**:175, 1945.
16. Macklin, M. T., and Macklin, C. C., Malignant interstitial emphysema of lungs and mediastinum

as important occult complication in many respiratory diseases and other conditions, Medicine **23**:281, 1944.

17. Forbes, G. B., Salmon, G., and Herweg, J. C., Further observations on post-tracheotomy mediastinal emphysema and pneumothorax, J. Pediat. **31**:172, 1947.
18. Salmon, G. W., Forbes, G. B., and Davenport, H., Airblock in newborn infant, J. Pediat. **30**:260, 1947.
19. Neffson, A. H., Tracheotomy in cases of acute obstructive non-diphtheritic infections of larynx, trachea and bronchi, Arch. Otolaryng. **36**:773, 1942.
20. Behnke, A. R., Jr., Physiologic studies pertaining to deep sea diving and aviation, especially in relation to fat content and composition of body, Bull. New York Acad. Med. **18**:561, 1942.
21. Bean, J. W., Effects of oxygen at increased pressure, Physiol. Reviews **25**:1, 1945.
22. Comroe, J. H., Dripps, R. D., Dumke, P. R., and Deming, M., Oxygen toxicity, J.A.M.A. **128**:710, 1945.
23. Hulpieu, H. R., and Cole, V. V., Effect of humidity and temperature on oxygen toxicity, J. Lab. and Clin. Med. **29**:1134, 1944.

SPANISH ABSTRACT

Crup Infeccioso II. Crup "Virus"

El llamado "virus," o crup no bacteriano, ocurrió en 87% de 347 casos de crup infeccioso. La patologia de la enfermedad es distinta de crup debido al H. influencia tipo B, o crup difterico. Clinicamente, el crup "virus" es una enfermedad progressiva con diseminación descendente de la infección en el traco respiratorio. La inflamación puede extenderse a varias regiones resultando en formas clinicas de la enfermedad conocidas como laringitis, laringotraqueites o laringotraqueopneumonitis. La mortalidad aumenta a medida que la enfermedad se disemina hacía abajo.

No hay un tratamiento especifico bien fundado para el crup "virus." Sin embargo deben administrarse sulfadiazina a todos los pacientes de crup infeccioso, hasta que los cultivos de la rinofarinx y sangre aseguerón la ausencia de potenciales patogenos. De hacerse quimioterapia continuado a todos los pacientes gravemente afectados por la enfermedad.

La mas frecuente complicación grave del crup "virus" es alguna forma de aire extra-alveolar intratoracico. La mas común causa de muerte es agobio respiratorio.

789 *Howard Ave.*

PRIMARY DIFFUSE PARATHYROID HYPERPLASIA IN AN INFANT OF FOUR MONTHS

By ROBERT N. PHILIPS, M.D.
San Francisco, Calif.

AMONG the reported cases of primary hyperparathyroidism, those due to diffuse hyperplasia are relatively uncommon.[1] Recently, Pratt et al[2] described a clinically studied case of hyperparathyroidism beginning in early infancy, with postmortem evidence of primary diffuse hyperplasia of the parathyroids. Previously, Landon[3] had reported a child with hypercalcemia and cystic bone changes, presumably present at six months of age. Surgical exploration at three years failed to reveal a parathyroid adenoma. Partial parathyroidectomy was done and subsequently the patient appeared cured. Ansbach and Clifton[4] reported a three-month-old infant with evidence of hyperparathyroidism in which operation was not done. Response to radiation therapy suggests that this may have been an adenoma of the parathyroid. The following case shows many of the features described by Pratt as well as some interesting differences.

CASE REPORT

The patient was a 16-week-old, white, male infant who was admitted to Babies Hospital because of congenital heart disease and a disturbance of bones. The parents were Jewish and first cousins, the mother's father and the father's mother being brother and sister. The patient was the result of the mother's first pregnancy.

The pregnancy was normal and terminated in a full-term forceps delivery of a 3430 gm. infant after a 13 hour labor. There was no jaundice nor cyanosis during the neonatal period. The chest was slightly sunken at birth. Appetite was poor and remained so until the time of admission. After numerous preliminary changes the formula was established as Lactogen, 90 cc., every three hours with 25 mg. ascorbic acid and three drops of a vitamin D preparation (250 I.U. per drop) in each feeding. At six weeks of age, the patient received iron and transfusions as treatment for anemia with only temporary improvement. Later, vitamin B injections were given without appreciable benefit. About two weeks before admission the patient appeared more ill than usual, refused feedings and began to cough. His physician first noted a heart murmur at this time. Roentgen studies showed "abnormal" bones. He was referred to Babies Hospital for study. He was brought by automobile over a four-day period of travel during extreme hot weather. During the trip the baby became progressively worse. His urine, which had previously been normal in color and amount, became dark although the flow remained adequate.

On admission the patient appeared on the verge of death, dehydrated, pallid and unresponsive. Temperature was 40.3° C. Respirations were shallow and irregular. There was moderate craniotabes. The sternum and attached cartilages were depressed forming a sharp angulation at the costochondral junctions. Aeration was impaired in the left lower lobe where fine crackling rales could be heard. There was a low-pitched systolic murmur. Liver, spleen and both kidneys were palpable. In spite of treatment with penicillin, sulfadiazine, intravenous fluids, plasma, blood and oxygen, the patient died 30 hours after admission.

Laboratory examination showed Hgb. 6.2 gm./100 cc., RBC 2.9 million, WBC 11.0 thousand, of which 50% were polynuclear leukocytes. Blood smear showed marked hypochromia and anisocytosis. Many of the red blood cells were stippled. The urine had a pH of 6.0. It contained 2+ albumin. The urinary sediment contained 10 to 15 mixed granular casts as well as 1 to 3 white

From the Pathological Laboratory of Babies Hospital and the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, New York, N.Y.
(Received for publication May 24, 1948.)

blood cells and 0 to 1 red blood cells per high power field. Bacteriologic examination of the blood, nose and spinal fluid revealed no growth. There were many organisms of the Esch. coli group cultivated from the pharynx. Blood chemical determinations revealed NPN of 64 mg./100 cc., serum chlorides of 114 mEq/1., serum calcium of 22.9 mg./100 cc., and a total serum protein of 4.37 gm./100 cc. of which 2.88 gm. was albumin and 1.49 gm. globulin. Roentgen studies (Figs. 1, 2 and 3) showed extensive osteoporosis of the entire skeleton with coarsening of the texture and many destructive changes, particularly at the ends of the shafts of the long bones. The provisional zones of calcification were well calcified. There were no signs of active rickets. Bone age was normal.

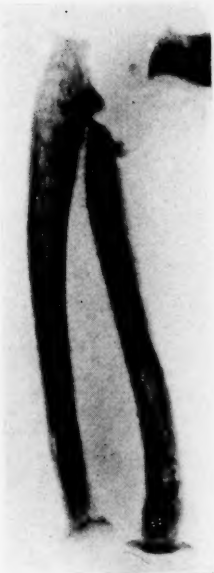


FIG. 1. Right radius and ulna. Note generalized decreased radiodensity and coarse pattern.

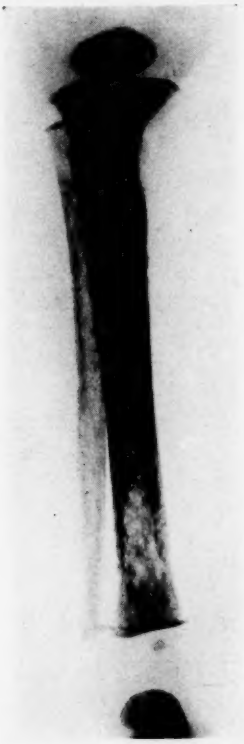


FIG. 2. Right tibia and fibula. Note good calcification at epiphyseal line and absence of rickets.

Autopsy showed a fairly well-developed but emaciated, white, male infant weighing 4,420 gm. and measuring 61 cm. in length, with marked craniotabes. Appearance of the thorax was striking and bizarre. Sternum and attached cartilages were depressed 1 to 2 cm. in relation to the ends of the ribs. There was a sharp, S-shaped angulation of each cartilage just before the costochondral junction. Serous cavities contained a moderate excess of clear pale fluid.

Pertinent gross findings were limited to the lungs, kidneys, parathyroids and bones.

Lungs were pale pink and showed small hemorrhages beneath the pleura and on the cut surface. They were moist but crepitated well and floated in water. The trachea and major bronchi contained a soft, grey friable exudate.

Kidneys were slightly enlarged. The left weighed 25 gm. (normal 19 gm.), right 28 gm. (normal 20 gm). Capsules stripped easily revealing a pale, slightly pebbly surface. On section, cortex appeared narrow, measuring 1.5 to 2.0 mm. thick. Glomeruli could be distinguished as tiny glistening points.

Right upper and lower parathyroids lay posterior to the thyroid. They were large and red in color. They weighed 31.5 and 33.2 mg. respectively. Each gland was approximately ten times the normal weight for the age.[5, 6] Left upper parathyroid was in the normal position and appeared small and pale. It weighed 4.7 mg. which is only slightly larger than normal for the age. Left lower parathyroid was identified in the prevertebral fascia after the removal of the larynx and esophagus. It was not weighed but appeared similar in size to the right parathyroids.

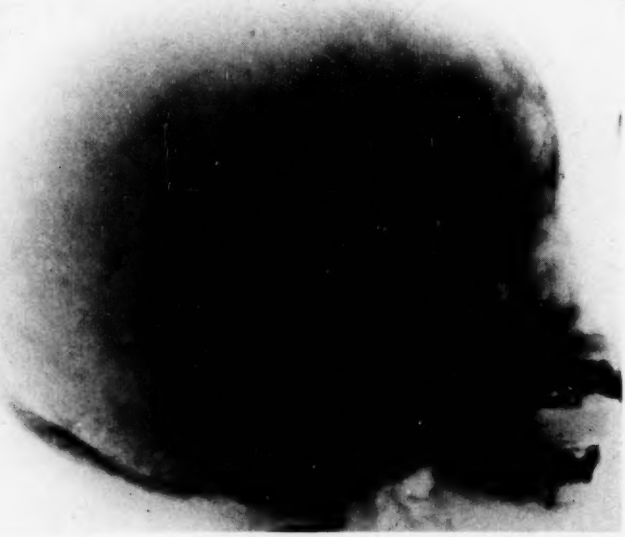


FIG. 3. The skull. Calcification of teeth is normal but lamina dura has disappeared.

The marrow of the rib, vertebral body and femur appeared pale. The epiphyseal line at the distal end of the femur was straight. Just proximal to the line, a 1 mm. zone of pinkish-white tissue was seen. The costochondral junction was wide and irregular. There were islands of cartilage partially surrounded by yellowish tissue, some of which was calcified (Figure 4).

There were no gross changes of the thymus, brain or pituitary.

Microscopic examination of the lungs showed good expansion but the alveoli contained many large cells with large pale nuclei and abundant, eosinophilic, foamy or vacuolated cytoplasm. Many multinucleated forms were present. In addition, the alveolar spaces contained considerable irregular, eosinophilic material which often had the arrangement of a hyaline membrane. A few polynuclear leukocytes and varying degrees of hemorrhage were likewise present. There were numerous calcium deposits, confirmed by von Kossa stains, within the alveolar and ductular walls, in the ductular epithelium and in the hyaline membrane (Figure 5). The bronchial and tracheal mucosa were largely destroyed and the deeper layers infiltrated with acute and chronic inflammatory cells. Many of the bronchial cartilages were partially and irregularly calcified.

On microscopic examination of the kidneys, most of the glomeruli appeared normal. A few were shrunken and replaced by hyaline masses. Others were large but bore hyaline deposits in some of their tufts. Some of these hyaline deposits were calcified. Occasionally, a Bowman's capsule was thickened and contained calcium. The convoluted tubules were dilated and contained an occasional

cast. Rarely, the cast, the tubular epithelium, or the basement membrane showed calcium deposition. Some of the collecting tubules showed similar calcification. Focal areas of erythrocyte generation were present in the cortex. The calyces and large renal vessels were normal.

On microscopic examination, all four parathyroid glands appeared similar. The gross increase

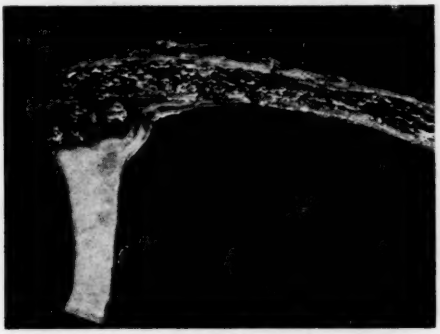


FIG. 4. Sharp angulation of rib with widening and distortion of costochondral junction.

in size of three of the glands was apparently due chiefly to an increase in the number of parenchymal cells but in part also to enlargement of some of the cells. The architecture was orderly. The parenchymal cells were arranged in irregular cords and occasionally formed pseudo-acini, separated by a few strands of connective tissue. There was a slight tendency toward basal arrangement of the nuclei. The parenchymal cells were polyhedral and of medium size with round darkly staining nuclei about the size of a lymphocyte nucleus. The cytoplasm was abundant but varied somewhat in amount. Most of the cells contained variable amounts of pink, granular material in their cytoplasm. Many of them, however, had relatively clear cytoplasm (Figure 6). No oxyphile cells or fat cells were present.

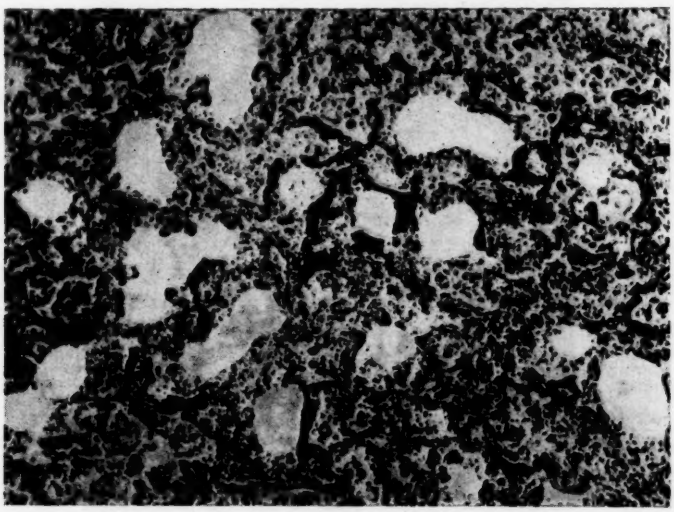


FIG. 5. Low power view of lung (von Kossa stain) showing calcifying hyaline membrane pneumonia.

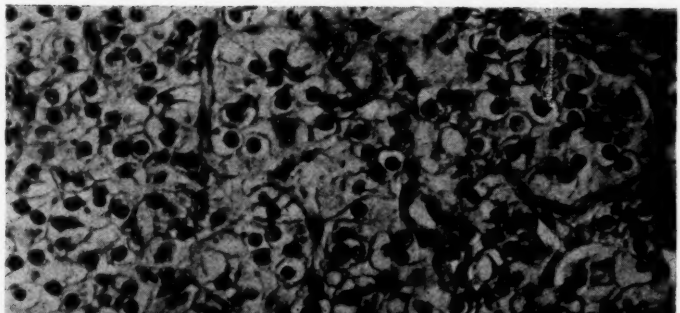


FIG. 6. High power view of parathyroid. Note large cells with abundant clear cytoplasm.

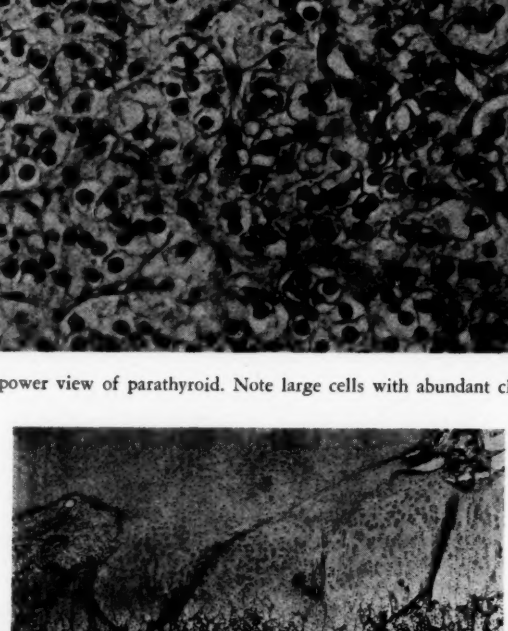


FIG. 7. Low power view of distal femoral epiphyseal line and diaphysis. Bony trabeculæ appear black. Note extensive marrow fibrosis between them.

Microscopically, the distal femoral epiphysis (Figure 7) showed a wide zone of proliferating cartilage in which the cell columns were slightly irregular. In the region between the resting and proliferating cartilage, there was a deep invagination of the perichondrium, forming a niche on each side of the chondral portion of the bone. These niches were filled with fibrous tissue. Between them, the cartilage contained several irregular endothelial-lined spaces which appeared to communicate with the shaft or the marrow cavity of the epiphysis. Some of these spaces were filled with loose connective tissue. Surrounding these spaces and beneath the invaginations on the surface there was a narrow zone of cartilage which took the eosin stain, suggesting altered structure.

At the epiphyseal line, the cartilaginous trabeculae were irregular and calcification was uneven, often sparing the central zone. The trabeculæ bore a small amount of osteoid tissue, and were lined by unusual numbers of osteoblasts. The marrow spaces were filled with loose fibrous tissue containing many osteoblasts and giant cells. Except for a minute focus near the epiphysis, no areas of blood formation were seen. The bony trabeculæ in the shaft were irregular in size and somewhat so in arrangement. The marrow cavity of the epiphysis showed similar but less extensive fibrosis, so that some blood forming tissue persisted. The findings in the rib and vertebræ were similar although areas of blood formation were more numerous.

The thymus showed microscopic calcification in many of the Hassal's corpuscles. The brain was normal microscopically except for the presence of a small amount of calcium in the stroma and blood vessel walls of the choroid plexus. The pituitary showed larger numbers of acidophilic cells than are usually seen in a casual section.

Gross and microscopic examination of the heart, spleen, liver, gall bladder, pancreas, adrenals, urinary bladder, prostate, testes, gastrointestinal tract, thyroid and spinal cord revealed no findings of note.

Discussion

The findings of marked hypercalcemia, enlargement of at least three of the parathyroid glands, generalized osteitis fibrosa, and calcium deposits in the kidneys, lungs, bronchial cartilage, thymus and choroid plexus are indications of hyperfunction of the parathyroid glands. The early onset of symptoms and the extensive anatomic changes suggest the possibility of a congenital origin. Although the left upper parathyroid was not grossly enlarged, it was histologically identical with the other three glands.

Primary diffuse parathyroid enlargement is usually considered to have a specific histologic appearance: namely, that all the cells are of the large water-clear type. Enlargement due to chronic renal disease shows, in contrast, only small, "chief" cells with interstitial fibrosis.[7] Kaplan,[8] after studying the parathyroids in 235 infants, suggested that the first changes of hyperfunction are swelling of the parenchymal cells and that shrinkage and fibrosis occur later. Thus, the parathyroids in Pratt's case[2] and in the present case may contain relatively few water-clear cells because they are in earlier stages of hyperfunction than the typical adult cases of primary diffuse hyperparathyroidism.

The bone changes are worthy of comment. Although the histologic appearance was similar to that of Pratt's case, the present case showed more striking gross and roentgenographic changes. Whether this was due to less adequate calcium intake or absorption[1] remains problematical. Marrow fibrosis was so extensive that it may have been partially responsible for this patient's severe and persistent anemia.

In any case of diffuse parathyroid enlargement, the possibility of primary renal disease must be considered. In an infant, the absence of congenital malformations of the urinary tract or chronic renal infection makes this unlikely. Moreover, only a relatively few nephrons showed anatomic abnormalities. Tubular and interstitial calcifications in the kidneys of infants occurs with considerable frequency in a variety of conditions.[9] Glomerular calcification is unusual although the other glomerular changes which were present have previously been described in hyperparathyroidism.[10]

The absence of arterial calcifications and the presence of a calcifying hyaline membrane pneumonia were additional noteworthy features.

Summary

A case is reported of primary diffuse hyperplasia of the parathyroids in a 16-week-old infant. The findings included generalized osteitis fibrosa and calcification in the kidneys, lungs, thymus, bronchial cartilage and choroid plexus.

References

1. Cope, O., Endocrine aspect of enlargements of parathyroid glands, Surgery **16**:273, 1944.
2. Pratt, E. L., Geren, B. B., and Neuhauser, E. B. D., Hypercalcemia and idiopathic hyperplasia of parathyroid glands in infant, J. Pediat. **30**:388, 1947.
3. Landon, J. F., Parathyroidectomy in generalized osteitis fibrosa cystica, J. Pediat. **1**:544, 1932.
4. Anspach, W. E., and Clifton, W. M., Hyperparathyroidism in children, Am. J. Dis. Child. **58**:540, 1939.
5. Andersen, Dorothy H., and Schlesinger, E. R., Renal hyperparathyroidism with calcification of arteries in infancy, Am. J. Dis. Child. **63**:102, 1942.
6. Andersen, Dorothy H., Unpublished data.
7. Anderson, W. A. D., Hyperparathyroidism and renal disease, Arch. Path. **27**:753, 1939.
8. Kaplan, E., Parathyroid gland in infancy, Arch. Path. **34**:1042, 1942.
9. Anderson, W. A. D., Renal calcification in infancy and childhood, J. Pediat. **14**:375, 1939.
10. Albright, F., Baird, P. C., Cope, O., and Bloomberg, E., Studies on physiology of parathyroid glands; renal complications of hyperparathyroidism, Am. J. M. Sc. **187**:49, 1934.

Spanish Abstract

Hiperplasia Paratiroides Fundamental Difusa en un Infante de Cuatro Meses

Un varoncito de cuatro meses, nacido de padres judíos consanguíneos, fué admitido en el Hospital de Niños. Tenía dificultades persistentes con la alimentación, padecía de anemia y los huesos eran anormales. El infante estaba deshidratado y febril. Habían moderadas cráneotabes. El esternón y los cartílagos pegados estaban marcadamente deprimidos. Habían estertores sobre el lóbulo izquierdo del pulmón. A pesar de administrarle oxígeno, penicilina, sulfadiazina y flúidos intravenos, el paciente murió 30 horas después de haber sido admitido. Los análisis de laboratorio mostraron una anemia hipocrómica severa; alto grado de nitrogeno sin proteina en la sangre y un suero calcio de 22.9 mg./100 cc. Por medio de radiografías se pudieron ver ósteoporosis general en todo el esqueleto con tosquedad de textura y muchos cambios destructivos, particularmente en las puntas de las cañas de los huesos largos. Las zonas provisionales de calficación estaban bien calcificadas. No habían señas de raquitismo activo. La edad de los huesos era normal.

La autopsia reveló un agrandamiento de la paratiroides diez veces su tamaño, octeitis fibrosa general y depósitos de calcio en los riñones, pulmones, el cartílago bronquial, timo y plexo coroideo. Había neumonía de la membrana hialina calcificante. Fuera de los depósitos de calcio que habían en el parénquima, los riñones estaban normales, indicando que ésta era una hiperplacia fundamental de la paratiroides. Se han registrado tres casos anterios de hiperparatiroidismo en la infancia.

University Hospital Medical Center

THE RELATIONSHIP OF FIBROCYSTIC DISEASE OF THE PANCREAS TO A DEFICIENCY OF SECRETIN

By ARCHIE H. BAGGENSTOSS, M.D., MARSCHELLE H. POWER, PH.D., AND JOHN H. GRINDLAY, M.D.
Rochester, Minnesota

IN RECENT histopathologic studies of the pancreas,[1,2] the occurrence of a remarkable degree of dilatation of the acini, flattening of the lining epithelial cells and inspissation of secretion has been described in a variety of pathologic states. The histologic appearance of the lesion is similar to that observed in the early stages of fibrocystic disease of the pancreas in children. The lesion has occurred with a high incidence in persons dying of uremia, carcinoma of the stomach, obstruction of the small intestine, chronic ulcerative colitis and sepsis.

On the basis of analysis of the cases and a review of pertinent experimental work, it was concluded that the following factors are important in the pathogenesis of this lesion in adult persons. First, there is inhibition of the type of pancreatic secretion normally stimulated by secretin. This inhibition may be brought about by vomiting,[3] by distention of the stomach,[4] or by mental discomfort.[5] Second, there is nervous stimulation of the pancreas, leading to depletion of zymogen granules and formation of a thick, viscid juice.[6-8] Third, there is dehydration which results in inspissation of the juice and the development of intrinsic obstruction. Finally, there is malnutrition (deficiency of protein), resulting in failure of reparative protein synthesis in the cells of the pancreatic acini.[9-11]

Because of the similarity of the histologic appearance of the pancreas in these cases to that observed in the early stages of so-called fibrocystic disease of the pancreas, and because inhibition of secretin stimulation seemed to be an important factor in the production of the lesion in adult persons, it was postulated that a congenital deficiency of secretin is responsible for fibrocystic disease of the pancreas in children. This deficiency may be the result of (1) congenital absence (relative or complete) of secretin, (2) a defect in the mechanism of secretin release from the intestinal mucosa or (3) destruction of secretin by abnormal amounts of secretinase in the blood. The present study is concerned only with the first possibility.

THEORY OF CONGENITAL DEFICIENCY OF SECRETIN IN FIBROCYSTIC DISEASE OF PANCREAS

The hypothesis that a congenital deficiency of secretin is responsible for the development of fibrocystic disease of the pancreas is based upon the concept first suggested by Blackfran and Wolbach,[12] and supported by Farber[13] and Andersen and Hodges,[14] that fibrocystic disease of the pancreas is the result of an abnormally thick and inspissated acinar secretion. If it is postulated that what occurs is an inhibition or an absence of stimulation of the pancreas by secretin, the only stimuli to secretion would be nervous

From the Section on Pathologic Anatomy, Mayo Clinic, and the Divisions of Biochemistry and Experimental Medicine, Mayo Foundation.
(Received for publication June 1, 1948.)

and that recently ascribed to pancreozymin. Such an imbalanced stimulation of the pancreas would result in a thick viscid juice. Stimulation of the pancreas by secretin has been described as causing a flow of alkaline fluid which serves to flush the alveoli, to thin the juice rich in organic material and to sweep it along the ducts. In the absence of the diluting and flushing effect of secretin, the thick viscid juice produced by nervous and pancreozymin stimulation might readily undergo stasis and inspissation, obstruct the ductules and acini, and lead to atrophy and fibrosis.

Any satisfactory hypothesis of the pathogenesis of fibrocystic disease of the pancreas must explain the varied clinical and pathologic manifestations of the disease. As Andersen and Hodges have pointed out, such hypothesis will have to take into account the following phenomena concerning the pancreatic lesion: (1) it is present at birth in most, if not all, cases; (2) the lesion is not a true malformation, but manifests itself late in pregnancy; (3) cystic fibrosis has a progressive nature.

If the lesion is the result of a congenital deficiency of secretin, it would be present at birth; the lesion would not be a true malformation but would manifest itself late in pregnancy, when the exocrine portion of the pancreas has developed enough to function; and finally, the lesion would have a progressive nature. The accumulation of thick, inspissated secretion would be progressive, and the resulting intrinsic obstruction would lead to progressive dilatation of pancreatic ducts and acini and finally, to atrophy and fibrosis. Nutritional, particularly protein, deficiencies probably also contribute to the progression of the pancreatic lesion. Gilbert and Gillman,[9] Gillman and Gillman,[10] and Friedman and Friedman[11] have produced pancreatic changes similar to those of fibrocystic disease in rats by feeding protein-deficient diets. We feel that in fibrocystic disease of the pancreas a congenital deficiency of secretin probably is the primary factor, and that chronic malnutrition resulting from loss of pancreatic function leads to a progression and intensification of the lesion. Among the other clinical and pathologic manifestations of the disease are the following: Congenital intestinal obstruction (meconium ileus), lesions of the liver and biliary passages, and lesions of the respiratory tract.

Each of these manifestations will be considered separately.

Congenital intestinal obstruction: The best explanation for the primary lesion in these cases is that of Farber,[13] who has accumulated evidence that the obstruction is the result of inspissated meconium. This inspissation, in turn, results from increased viscosity of the meconium brought about by lack of pancreatic digestion. The frequent occurrence of volvulus and the occasional occurrence of peritoneal bands have been attributed by Andersen and Hodges[14] to the hypermotility of the intestine and peritoneal irritation which may occur after obstruction by meconium. These interpretations appear to have a sound basis. In the presence of a congenital deficiency of secretin, pancreatic digestion would be insufficient to prevent inspissation of meconium and subsequent intestinal obstruction. The fact that there is good evidence that secretin stimulates the flow of succus entericus[15] is an additional indication that deficiency of secretin plays an important role in the production of meconium ileus. The reduction of a normal flow of succus entericus and the resulting deficiency of the enzymes present in this juice would be additional factors contributing to the inspissation of meconium.

Lesions of the liver and biliary passages: The lesions in the liver are generally described as local areas of cirrhosis which histologically consist of a concentration of small

bile ducts containing eosinophilic concretions and surrounded by fibrous tissue. These lesions have been interpreted as constituting evidence of intrahepatic and partial biliary obstruction. Hypoplasia of the gallbladder and atresia of the cystic duct are other observations frequently made. All these lesions have been attributed to abnormal secretion by the liver and biliary tract. Normally, secretin stimulates the flow of bile. If the supply of secretin was congenitally deficient, a reduction in volume of the bile and possibly also a change in its quality might be expected. This could account for inspissation of secretion and local areas of biliary obstruction. If the flow of bile was reduced, there might not be sufficient bile to distend the gallbladder and stimulate contraction. In the absence of normal function, normal development often is inhibited.

Lesions in the respiratory tract: These lesions consist of chronic suppurative bronchitis, bronchiectasis, abscesses and bronchopneumonia. The pulmonary lesions have been attributed to congenital bronchiectasis, to deficiency of vitamin A secondary to steatorrhea, to an abnormality in the bronchial secretions comparable to that believed to cause the pancreatic lesion, or to an infection of unknown nature which involves both the pancreas and the lungs. The evidence against these theories has been clearly outlined by Andersen and Hodges,[14] and we are in agreement with their conclusion that the pulmonary lesions are secondary to the nutritional disturbances, including deficiency of vitamin A resulting from lack of pancreatic function. We believe the same interpretation holds for the occasional occurrence of dilatation of ducts and inflammation of the salivary glands. Since a congenital deficiency of secretin would result in a diminution of pancreatic function, it would consequently be the basis for the lesions discussed above.

Other Theories as to Origin of Fibrocystic Disease of Pancreas

The foregoing are the theoretic considerations which led to the hypothesis that a congenital deficiency of secretin is responsible for fibrocystic disease of the pancreas. In our opinion, this hypothesis more nearly adequately explains the varied clinical and pathologic manifestations of this disease than do any of the current theories.[16] Of these current theories, the most reasonable ones are those which postulate obstruction of the pancreatic ducts and acini. Obstruction as an etiologic factor may be considered under these subdivisions: (1) obstruction of ducts as a result of deficiency of vitamin A (squamous metaplasia), (2) congenital stenosis or atresia of ducts, and (3) obstruction of acini and ductules by an abnormal secretion.

Deficiency of vitamin A: The most important facts against the theory that deficiency of vitamin A is an etiologic factor are these: (1) in most cases either there is no squamous metaplasia of the pancreatic ducts or the amount is insufficient to cause obstruction, (2) deficiency of vitamin A of severe degree may not be accompanied by pancreatic lesions,[12] and (3) there is no evidence that prenatal deficiency of vitamin A is a causative factor.[17]

Obstruction of ducts by congenital stenosis or atresia: There are a few cases[18,19] of fibrocystic disease of the pancreas in which obstruction of the pancreatic ducts has been demonstrated. Both Andersen[14] and Farber,[13] however, agreed that congenital atresia of the main ducts is uncommon. One of us[20] examined serial histologic sections of the entire pancreas in two cases without finding evidence of stenosis or atresia of the ducts. Collett[21] recently has examined sections of the pancreas in this manner in two cases and has been unable to show stenosis or atresia of the ducts in either of them.

Obstruction of acini and ductules by an abnormal secretion: This theory has already been mentioned herein. It has been accepted by those who have had the most experience with the disease. Farber[13] has extended the theory to include other epithelium-lined organs and has stated that in many cases dilatation of glands and inspissation of secretion in the trachea, bronchi, esophagus, duodenum, gallbladder, salivary glands and jejunum are evident. In the cases reported by one of us, occasional distention of the bronchial glands by mucus and dilatation of glands of the duodenum were the only glandular changes observed[20] exclusive of those in the pancreas. In observations made prior to these reports, only mild dilatation of the acini of the salivary glands[19,22] was described. That the pancreatic secretion obtained by duodenal drainage is thick and inspissated in these cases has been demonstrated, however, by Farber. He suggested that a disturbance of parasympathetic innervation or an autonomic imbalance in nervous control of secretions in the pancreas and in mucous glands might be responsible. According to Farber,[8] the pancreatic lesion of fibrocystic disease can be reproduced in kittens by the injection of pilocarpine over a period of two to eight weeks. There is, however, no direct evidence that patients who have fibrocystic disease of the pancreas are subject to abnormal parasympathetic stimulation.

Testing of Theory of Congenital Deficiency of Secretin

It is our opinion that the pancreatic, hepatic and intestinal lesions described as accompanying this disease can be explained more satisfactorily by a deficiency of secretin stimulation of the pancreas. If this hypothesis is employed, it becomes unnecessary to postulate the existence of an abnormal parasympathetic innervation or an autonomic imbalance in the nervous control of secretions. As has already been pointed out, if the flushing and diluting action of secretin stimulation was absent, secretory pressure would be low and it could be expected that the thick, viscid secretion resulting from normal nervous and pancreozymin stimulation would collect in the acini and ducts. Stasis and dehydration might then occur. Inspissation of the secretion, obstruction of the acini and ductules, atrophy and fibrosis could then be expected to follow.

To test this hypothesis, it was necessary to determine: (1) that secretin could be extracted consistently from specimens of the upper part of the intestinal tract obtained at necropsy, and (2) that secretin is absent in specimens of the upper part of the intestinal tract among patients dying of fibrocystic disease of the pancreas.

The first requirement has recently been met.[23] The second requirement has been met in the single case of fibrocystic disease of the pancreas which we have had the opportunity to study. Up to the present writing, we have been able to extract secretin (S_1) according to the methods outlined by Ivy and his co-workers[24–26] from specimens of the upper part of the intestinal tract in 17 of 18 adult persons. The single failure occurred in a case in which a patient who had carcinoma of the uterus died of intestinal obstruction of four weeks' duration. We have also been able to extract secretin consistently from the upper part of the intestinal tracts of all children (13 cases) except premature and newborn infants and except a single infant who had fibrocystic disease of the pancreas. The specimen (duodenum and upper part of the jejunum) from this patient was sent to us through the courtesy of Dr. J. P. Simonds and Dr. H. F. Philipsborn of Children's Memorial Hospital, Chicago. The child was 16 months old; necropsy was performed ten hours after death. The specimen was packed in dry ice and sent to us by air express.

When the specimen arrived, it was found to be frozen solidly. Extraction was begun immediately. The final extracted materials (S_1) weighed 12.4 mg. When it was injected intravenously into a dog with a total pancreatic fistula, there was no secretory response.

In all the other successful extractions, active preparations could be obtained from persons whose age varied from two months to 73 years. The extraction was successful when it was carried out as late as 15 hours postmortem. It was found that by keeping the specimen of the upper part of the intestinal tract in the frozen state, extraction could be delayed as long as 39 days without loss of secretory activity. The dose of the final extracted material (S_1) necessary to bring about a satisfactory secretory response in the dog with a total pancreatic fistula varied from 1 to 50 mg., depending on the type of case, the postmortem interval and the dog. In all but four cases, 10 mg. was sufficient to provoke a satisfactory response.

Although we were unable to extract an active preparation from infants in the neonatal period, we found that by combining the extracts obtained from three premature infants and, in another instance, from three newborn infants, we were able to obtain a satisfactory secretory response. This indicates that secretin is present in the neonatal period, but that the amounts probably are so small that they are lost during the process of extraction when individual specimens are used.

Congenital Deficiency of Secretin and Hormone Deficiency States

We are hoping to obtain a sufficient number of specimens of the upper part of the intestinal tract from persons with fibrocystic disease to enable us to test our hypothesis thoroughly before we arrive at a final conclusion. We feel, however, that the results of this study lend considerable support to the hypothesis that fibrocystic disease of the pancreas is the result of a congenital deficiency of secretin. If this proves to be true, the disease will be comparable to other hormone deficiency diseases such as diabetes, hypothyroidism and hypopituitarism. In these diseases the degree of hormonal deficiency varies considerably, and alters the clinical characteristics. It is reasonable to suppose that the degree of deficiency of secretin also will be variable, and that we will encounter patients with only mild degrees of secretin deficiency and correspondingly milder degrees of damage to the pancreas. It is conceivable that we shall be able to extract secretin from those patients who have fibrocystic disease in which there is only a mild deficiency of secretin. If further investigation suggests such a relative deficiency, rather than a complete absence of secretin, it will become necessary to work out some method for the quantitative estimation of the secretin content of the intestinal mucosa.

Hereditary Considerations

Recently, Andersen and Hodges[14] ascertained that cystic fibrosis of the pancreas occurs in families in a manner consistent with the behavior of a hereditary trait. They concluded that cystic fibrosis of the pancreas represents the commonest manifestation of a hereditary disease which may also involve the intestinal glands, the intrahepatic bile ducts, the gallbladder and, occasionally, other epithelial glands, and which has as its primary feature the production of abnormal secretion of these glands, the morphologic features being secondary. With these considerations and interpretations we are in agreement, and we should like to suggest that the congenital defect responsible for the disease is a deficiency of secretin.

Therapeutic Considerations

The therapeutic implications of this hypothesis are interesting and important. If it is proved that fibrocystic disease of the pancreas is the result of a congenital deficiency of secretin, will it become possible effectively to treat the condition in a manner similar to the effective treatment of diabetes with insulin? Although a complete answer obviously is not possible now, the available knowledge concerning the disease indicates a negative answer. Secretin, as indicated by its use as a diagnostic aid,[27,28] can elicit a secretory response only when the pancreas is intact and capable of functioning. In many cases of fibrocystic disease, however, the destruction of pancreatic parenchyma is extensive before a diagnosis has been made. In these cases the use of secretin could be of little or no therapeutic value. In fact, in the presence of irremovable obstruction of the large pancreatic ducts by plugs of inspissated secretion, the administration of secretin might, by causing a rupture of small ductules as a result of increased secretory pressure, lead to additional destruction of the parenchyma. In cases in which the disease process is in an early stage, with minimal parenchymal damage and without obstruction of the larger ducts, the administration of secretin might restore some semblance of normal secretory function and play an important part in the recovery of the patient.

It is of course obvious that no such therapeutic use of secretin should be undertaken until it has been completely proved that fibrocystic disease of the pancreas is the result of a deficiency of secretin. Even when this proof is available, other problems concerning the purity and the antigenic and other properties of secretin need to be thoroughly investigated before secretin can be used in the therapy of this disease.

Summary and Conclusions

The theoretic considerations which indicate that fibrocystic disease of the pancreas is the result of a congenital deficiency of secretin have been outlined. The varied clinical and pathologic manifestations of this disease can, in our opinion, be more nearly adequately explained by this hypothesis than by any of the other current theories. The absence of secretin (S_1) in the upper part of the intestinal tract of a patient with fibrocystic disease of the pancreas lends support to this theory; which is to say, that the condition is the result of a congenital deficiency of secretin. It has been shown to be possible to extract secretin from the upper part of the intestinal tract of persons two months to 73 years old. The only consistent failures occurred in work with patients in the neonatal period. Successful extraction of secretin from these patients in the neonatal period can be carried out, however, by combining the crude extracts obtained from a number of patients. The extraction of secretin is successful if it is done up to 15 hours postmortem. If the specimen is kept in a frozen state, extraction can be delayed without loss of activity as long as 39 days. Because this method of extraction is successful in individual cases at necropsy, it becomes possible to correlate the presence or absence of secretin with varying pathologic conditions. This, in turn, may open up a broad field for the investigation of many pancreatic and intestinal disturbances in addition to fibrocystic disease of the pancreas.

References

1. Baggenstoss, A. H., Pancreas in uremia; a histopathologic study, Am. J. Path. **23**:908, 1947.
2. Baggenstoss, A. H., Dilatation of acini of pancreas; incidence in various pathologic states, Arch. Path. (In press.)

3. Lagerlof, H. O., Pancreatic Function and Pancreatic Disease Studied by Means of Secretin, (Quoting Bernard, C.) The Macmillan Company, New York, 1942, p. 289.
4. Bizard, G., and Boulet, L., Influence de la distention de l'estomac sur la sécrétion pancréatique, Comp. rend. Soc. de. biol. **116**:196, 1934.
5. Farrell, J. I., and Ivy, A. C., Proof of humoral mechanism for external pancreatic secretion, Am. J. Physiol. **78**:325, 1926.
6. Babkin, B. P., Rubaschkin, W. J., and Ssawitsch, W. W., Über die morphologischen Veränderungen der Pankreaszellen unter der Einwirkung verschiedenartiger Reize, Arch. f. mikr. Anat. u. Entwcklngs. **74**:68, 1909.
7. Sergeyeva, Maria A., Microscopic changes in pancreatic gland of cat produced by sympathetic and parasympathetic stimulation, Anat. Rec. **71**:319, 1938.
8. Farber, S., Experimental production of achylia pancreatica, Am. J. Dis. Child. **64**:953, 1942.
9. Gilbert, Christine, and Gillman, J., Diet and disease in Bantu, Science **99**:398, 1944.
10. Gillman, T., and Gillman, J., Powdered stomach in treatment of fatty liver and other manifestations of infantile pellagra, Arch. Int. Med. **76**:63, 1945.
11. Friedman, S. M., and Friedman, C. L., Effect of low protein diet on structure of pancreas, Canad. M. A. J. **55**:15, 1946.
12. Blackfan, K. D., and Wolbach, S. B., Vitamin A deficiency in infants; clinical and pathological study, J. Pediat. **3**:679, 1933.
13. Farber, S., Pancreatic function and disease in early life; pathologic changes associated with pancreatic insufficiency in early life, Arch. Path. **37**:238, 1944.
14. Andersen, Dorothy H., and Hodges, R. G., Celiac syndrome, genetics of cystic fibrosis of pancreas with consideration of etiology, Am. J. Dis. Child. **72**:62, 1946.
15. Ågren, G., Über die pharmakodynamischen Wirkungen und chemischen Eigenschaften des Secretins, Scandinav. Arch. f. Physiol. **70**:10, 1934.
16. Wiglesworth, F. W., Fibrocystic disease of pancreas, Am. J. M. Sc. **212**:351, 1946.
17. Andersen, Dorothy H., Cystic fibrosis of pancreas and its relation to celiac disease, Am. J. Dis. Child. **56**:344, 1938.
18. Benoit, W., Hyperinsulinismus bei eingeborener Atresie des Pankreasganges, Endokrinologie **16**:313, 1935.
19. Oppenheimer, Ella H., Congenital atresia of pancreatic duct with cystic fibrosis of pancreas, Arch. Path. **29**:790, 1940.
20. Baggenstoss, A. H., and Kennedy, R. L. J., Fibrocystic disease of pancreas, Am. J. Clin. Path. **15**:64, 1945.
21. Collett, R. W., Personal Communication.
22. Wilson, J. R., and Dubois, R. O., Keratomalacia in infant, with postmortem examination, Am. J. Dis. Child. **26**:431, 1923.
23. Baggenstoss, A. H., Power, M. H., and Grindlay, J. H., Extraction of secretin from intestine of man, Gastroenterology, In press.
24. Ivy, A. C., Kloster, G., Drewyer, G. E., and Lueth, H. C., On preparation of "cholecystokinin," Am. J. Physiol. **91**:336, 1929.
25. Ivy, A. C., Kloster, G., Drewyer, G. E., and Lueth, H. C., Preparatiion of secretin concentrate, Am. J. Physiol. **95**:35, 1930.
26. Greengard, H., and Ivy, A. C., Isolation of secretin, Am. J. Physiol. **124**:427, 1938.
27. Maddock, Charotte L., Farber, S., and Shwachman, H., Pancreatic function and disease in early life; effect of secretin on pancreatic function of infants and children, Am. J. Dis. Child. **66**:370, 1943.
28. Philipsborn, H. F., Jr., Laurence, Grace, Gibson, S., and Greengard, H., Analysis of duodenal drainage in steatorrheas, J. Pediat. **26**:107, 1945.

SPANISH ABSTRACT

La Relación de la Enfermedad Fibrocística del Pancreas con una Deficencia de Secretina

Se detallan teorías que indican que la enfermedad fibrocística del pancreas resulta de una deficiencia de secretina congénita. Las diversas manifestaciones clínicas y patológicas de esta enfermedad se

pueden explicar más adecuadamente con esta hipótesis que con cualquier otra teoría corriente. La ausencia de la secretina (S_1) en el conducto intestinal superior de un paciente padeciendo de este enfermedad, sostiene esta teoría, es decir, que la condición resulta de una deficencia congénita de secretina.

Es posible extraer secretina del conducto intestinal superior de las personas de dos meses hasta 73 años de edad. Han ocurrido fracasos consecuentes en el período neonatal solamente. Se tiene éxito en la extracción de secretina de estos pacientes combinando los extractos crudos que se hayan obtenido de un número de pacientes. La extracción de la secretina se hace con buen éxito hasta quince horas después de muerta la persona. Si el espécimen se congela, la extracción se puede diferir hasta 39 días sin pérdida de actividad. Por ser este método de extracción de gran eficencia en casos individuales en la necropsia, es posible poner en correlación la presencia o la ausencia de la secretina con condiciones patólogicas variantes. Esto puede abrir un campo amplio para la investigación de muchos desordenes pancreáticos e intestinales además de la enfermedad fibrocística del pancreas.

Mayo Clinic

Pediatrics

VOLUME 2 OCTOBER 1948 NUMBER 4

AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

REPORT OF THE EXECUTIVE BOARD MEETING

Milwaukee, Wis., June 26 and 27, 1948

A meeting of the Executive Board was held at the Schroeder Hotel, Milwaukee, on Saturday and Sunday, June 26 and 27, 1948. The first session was called to order at 10 A.M. Saturday by the President, Dr. John A. Toomey. There were present Drs. Toomey, Beaven, Stringfield, Munns, Pease, Hurtado, Bost, London, Barba, McElhenny, Bruce, Sisson, Martmer and Grulee.

The following applicants were elected to fellowship:

District I: Isadore Gershman, Providence, R.I., and Arnold Gesell, New Haven, Conn.

District II: Kenneth M. Alford, Buffalo, N.Y., Alfred B. Amler, White Plains, N.Y., Edward Bailey, Jamaica, N.Y., Evelyn J. Basile, Brooklyn, N.Y., Marvin L. Blumberg, Forest Hills, L.I., N.Y., Nathan Cabot, New York, N.Y., John Newcomer DeHoff, Flushing, N.Y., Frank A. Disney, Rochester, N.Y., Emanuel Fletcher, Flushing, N.Y., Alfred L. Florman, New York, N.Y., Paul Freud, Forest Hills, N.Y., Harry Gibel, Brooklyn, N.Y., Arthur A. Goldfarb, New York, N.Y., A. Gerald Heller, Flushing, N.Y., Elizabeth B. Hinckley, New York, N.Y., Leo Jenkins, Long Island City, N.Y., Samuel F. Jenkins, New York, N.Y., Hilda Knobloch, New York, N.Y., Maurice Lenarsky, New York, N.Y., Sherman Little, Buffalo, N.Y., Hyman Merenstein, Brooklyn, N.Y., Rowland L. Mindlin, New York, N.Y., William Obrinsky, New York, N.Y., Benjamin Philips, Brooklyn, N.Y., Thomas B. Re, Brooklyn, N.Y., Allan A. Rubenstein, Laurelton, N.Y., Robert C. Schwartz, Syracuse, N.Y., Charles F. Shevlin, Jamaica, N.Y., Margaret Dorothy Schaffner Tenbrinck, New York, N.Y., Mark Joseph Wallfield, Brooklyn, N.Y., Donald Weisman, White Plains, N.Y., Irving B. Wexler, Brooklyn, N.Y., and Lucy M. White, Rochester, N.Y.

District III: John B. Bartram, Philadelphia, Pa., Charles P. DeFuccio, Jersey City, N.J., Bernard German, Newark, N.J., Robert J. Kressler, Philadelphia, Pa., Harry S. Mackler, Elizabeth, N.J., Roy Pollack, Cliffside Park, N.J., Anthony Joseph Repici, Haddonfield, N.J., Mary L. Richardson, Philadelphia, Pa., and Nathan Zukerberg, Newark, N.J.

District IV: Ogden C. Burton, Washington, D.C., Fred S. Gachet, Lakeland, Fla., Althea D. Kessler, Washington, D.C., J. Harry Lange, Atlanta, Ga., Ramon Fernandez Marchante, Santurce, Puerto Rico, John Oscar Rydeen, Norfolk, Va., and William C. Stifler, Baltimore, Md.

District V: Bernard B. Conway, Toronto, Ontario, Canada, Genevieve Delfs-Ewing, Youngstown, Ohio, Aaron R. Edwards, Ann Arbor, Mich., James Mace Harkey, Canton, Ohio, Edward W. McCall, Columbus, Ohio, Kenneth C. Macpherson, Detroit, Mich., Patrict John Maloney, Ottawa, Ontario, Canada, and Cathryn C. Rotondo, Louisville, Ky.

District VI: A. E. Cohen, Peoria, Ill., Michael Crofoot, Omaha, Neb., Richard E. Dukes, Urbana, Ill., Ely Epstein, Milwaukee, Wis., Hyman Harry Gordon, Chicago, Ill., L. Martin Hardy, Chicago,

Ill., Harry M. Levy, Chicago, Ill., Niels L. Low, Racine, Wis., Mildred A. Norval, Rochester, Minn., Julius B. Richmond, Chicago, Ill., and S. S. Snider, Chicago, Ill.

District VII: Anthony Louis Alfieri, Dallas, Tex., Benjamin Prestridge Clark, Gadsden, Ala., Louis S. Frank, Oklahoma City, Okla., William Carey Rivenbark, New Orleans, La., Alma Marie Sullivan, New Orleans, La., and James N. Walker, Fort Worth, Tex.

District VIII: Harry Baker, Vancouver, B.C., Canada, Gaston James Baus, Glendale, Calif., Edward E. Brown, Ashaland, Ore., Jack Merton Docter, Seattle, Wash., Arthur L. Esserman, Denver, Colo., Margit H. Grytbak, Seattle, Wash., William A. Jaquette, Jr., Seattle, Wash., Charles Kaplan, Seattle, Wash., Edgar L. Mariette, Glendale, Calif., Norman W. Murphy, Seattle, Wash., John M. Nelson, Denver, Colo., Wendell M. Redfern, Glendale, Calif., Charles C. Stevenson, Oakland, Calif. Paul Stone Strong, Los Angeles, Calif., and Reginald Alexander Wilson, Vancouver, B.C., Canada.

District IX: Pedro León Luque, Córdoba, Argentina, Vicente de Sampaio Lara, São Paulo, Brazil, Homero de Melo Braga, Curitiba, Paraná, Brazil, Carlos Prado, São Paulo, Brazil, Maria Clara Mariano da Rocha, Porto Alegre, Rio Grande do Sul, Brazil, Francisco Talaia de Moura, Porto Alegre, Rio Grande do Sul, Brazil, Jaime Jorge, Ciudad Trujillo, D.R., Rafael A. Miranda, Ciudad Trujillo, D.R., Fedirico de Miranda, Camagüey, Cuba, Antonio Bequez Cesar, Santiago de Cuba, Ramiro Valledor, Santa Clara, Cuba, and Alvar Carillo Gil, Cuernavaca, No. 134, Mexico.

Upon application the following were granted Emeritus Fellowship: George E. Dash, Boothbay, Me. (formerly Cincinnati, Ohio), Samuel Goldberg, Philadelphia, Pa., George Pratt Hunt, Pittsfield, Mass., Earl W. May, Detroit, Mich., and J. D. Stevenson, Beaver, Pa.

Honorary Fellowship was granted to Richard W. B. Ellis, Edinburgh, Scotland, and Alan Moncrieff, London, England.

Associate Fellowship was extended to Fe del Mundo, Manila.

The following resignations were accepted: James R. Wilson, Chicago, Ill., Alicia Armand Ugón, Montevideo, Uruguay, Miguel Angel Jaureguy, Montevideo, Uruguay.

At his own request, Frederick S. Huntington, Darien, Conn., was reinstated.

REPORT OF THE BUDGET COMMITTEE

The Budget Committee presents herewith the proposed budget for the fiscal year July 1, 1948, through June 30, 1949.

In connection with the budget and as a result of a careful survey of the finances of the Academy and policies which are related thereto, the Budget Committee makes the following recommendations:

1. That the President, Vice-President and members of the Executive Board be granted an allowance of five cents plus postage for each letter sent out from their respective offices. For this purpose the items 1, 2 and 3 totaling $600.00 has been included in the budget.
2. That the State Chairmen as at present be allowed a postage allowance for all correspondence relative to Academy matters. Item (4) amounting to $400.00 is included for this purpose; a portion of the $400.00 is to be available for special projects subject to approval of the Executive Board.
3. That a Contingency Fund be established to provide for requests for funds for special projects subject to approval by the Executive Board.
4. That the Reserve Fund be rehabilitated by the deposit therein of all initiation fees until the Reserve Fund shall equal the amount of the year's budget.
5. That any surplus which shall remain at the end of the fiscal year be allocated to the Reserve Fund until it shall equal one year's budget.
6. That deficit financing in preparing the budget be discontinued.
7. That meetings be arranged, whenever possible, so as to be self-supporting. Any profit which may accrue from meetings to be placed in the Reserve Fund until it shall equal one year's budget. Thereafter the profit from the previous year may be used to supplement revenue from the annual dues in preparing the following year's budget.
8. That the action of the Executive Board be reaffirmed in that no individual or committee shall obligate the Academy for an amount greater than the amount authorized by action of the Executive Board without official action by the Executive Board and that such action be transmitted to all Committee Chairmen as well as all members.

9. That the publication of the Treasurer's report shall be on the basis of the fiscal year. Such report to be ready for publication not later than October first.

ASSETS

May 31, 1948

	Par or Maturity	*Cost*
U.S.A. Savings Bonds—2½—Series G due June 1, 1953	$26,200.00	$26,200.00
DEFENSE BONDS—Series F—Due Oct. 1, 1953	2,500.00	1,850.00
DEFENSE BONDS—Series F—Due Jan. 1, 1954	5,000.00	3,700.00
Northern Trust Company—Principal on hand		77.10
State Bank & Trust Company—Checking Account		21,726.77
State Bank & Trust Company—Savings Account		15,143.33
First National Bank & Trust Company—Savings Account		9,130.85
		$77,828.05

LIABILITIES

May 31, 1948

Initiation Fees on deposit	$ 4,775.00	
ICH Committee*	21,113.81	
Post-War Courses Committee†	4,505.40	
Credit outstanding on members accounts	226.50	30,620.71
Net Assets		$47,207.34

* Checks received from members and firms, deposited in the checking account, to be used for the ICH Committee.

† Balance of money due Mead Johnson & Company.

PROPOSED BUDGET

(For the year ending June 30, 1949)

Secretary's Office

Salaries:		
Secretary	$18,000.00	
Assistant Secretary	5,000.00	
Office Manager	5,000.00	
Other Office Help	6,000.00	
Rent	3,000.00	
Treasurers' Bonds	350.00	
Postage	1,200.00	
Travel-Secretary	1,500.00	
Stationery & Printing	3,500.00	
Office Supplies & Equipment	500.00	
Incidentals	1,500.00	
Contingency	1,000.00	
		$46,550.00

Executive Board		8,000.00		
Secretarial Allowances:				
1. President	$100.00			
2. Vice-President	50.00			
3. 9 District Chairmen	450.00			
4. State Chairmen	400.00			
5. Contingency Fund	500.00	1,500.00		
Special Committees		3,000.00		
Emergency Fund		5,000.00		
			$17,500.00	$64,050.00

Estimated Income

2,188 members @ $20.00 per year	$43,760.00	
212 L.A. members @ $5.00 per year	1,060.00	
		44,820.00
Deficit		$19,230.00

ANNUAL MEETINGS

1942—Chicago, Ill.:	Receipts	$10,772.00	
	Expenses	8,781.31	
	Credit		$1,990.69
1944—St. Louis, Mo.:	Receipts	$11,152.00	
	Expenses	8,275.76	
	Credit		$2,876.24
1945—Detroit, Mich.:	Receipts	$12,703.00	
(Jan. 1946)	Expenses	8,592.71	
	Credit		$4,110.29
1946—Pittsburgh, Pa.:	Receipts	$19,150.24	
(Feb. 1947)	Expenses	17,072.82	
	Credit		$2,077.42
1947—Dallas, Texas:	Receipts	$19,382.00	
	Expenses	18,936.36	
	Credit		$ 445.64

* * *

1st Pan-American Congress Meeting—July 1947—Washington, D.C.			
	Expenses	$14,257.67	
	Receipts	6,723.00	
	Deficit		$7,534.67
Areal Meeting—September 1947—Salt Lake City, Utah			
	Expenses	$ 3,231.40	
	Receipts	2,299.50	
	Deficit		$ 931.90

RECEIPTS AND DISBURSEMENTS FOR THE ANNUAL MEETING—DECEMBER, 1947

Receipts			
Exhibits		$8,975.00	
Registration Fees		7,079.50	
Round Table Fees		2,165.00	
Seminar—Allergy		550.00	
Seminar—Blood		612.50	$19,382.00
Disbursements			
Printing			
Exhibit Material	$ 76.00		
Cards—Printed	4.00		
Stationery & Mimeograph paper	220.00		
Tickets	17.00		
Mimeo. Ex. Bd. Minutes	176.15		
Printing Gov. Certificates	39.00		
Hotel Applications	25.50		
Programs	1,100.00	1,657.65	
Postage		298.96	
Express		73.71	
*Program Expense		245.91	
Badges		354.00	
Hotel Expense		7,268.40	
Work on Hotel Reservations		430.72	
Reporting		449.03	
Publicity Expense		453.50	
Signs		47.35	
Speakers		4,144.44	
Expense of Secretary's Office		493.12	
Projectors & Screens, etc.		60.50	
Guard Service		192.00	
Miscellaneous			
Telephone, telegrams	136.47		
Office Supplies	48.77		
Help at Registration Desk	19.00		
Tips	50.00	254.24	
Seminar Expense		603.30	
Committee Lunches		856.00	
Exhibit Booths		724.50	
Round Table Expense		329.03	18,936.36
Balance			$ 445.64

* Included in General Budget.
(Total Expense of the Executive Board, $2,457.44)

REPORT OF THE SECRETARY

The Academy has had one of the most disturbing periods which it has ever gone through. The reason being that most unexpectedly the recommendation of the ICH Committee, that we apply to the government for funds for pediatric teaching, brought out a storm of protest from certain quarters. The Executive Board has met twice with respect to this since the original proposal has been adopted and has decided to place the whole thing for a vote at the Annual Meeting in Atlantic City this fall. This discussion has so overtopped other important activities in the Academy that perhaps some of them have been neglected.

The various committees are not only doing their jobs but in a large measure are doing them better than they ever did before. We are gradually developing some very competent groups within the Academy, who are taking over certain phases of the work of the Academy and doing an excellent job.

During the past four or five years, mainly because of increased activities, the Academy has spent more than it has taken in, and it will probably be necessary to increase the dues. Whether this increase is temporary or permanent will depend largely upon the outcome of certain enterprises in which we are at present involved, especially the new journal.

The new journal, PEDIATRICS, has got underway and is in every way a credit to the Academy. We should be especially grateful to Dr. Hugh McCulloch for all the work he has done. As to the finances, Dr. Lancaster has gone over this carefully with many people and seems to grasp the situation quite well. He too has put in a great deal of time.

We have overstepped ourselves to an extent by having too many meetings this year. While this is to some extent the fault of the Secretary, there are certain contributing factors which should be taken into account. We had expected, following our canvas of the situation, that we would have almost twice as many exhibitors at our areal meetings as we have had. There seems to have been a sudden retraction of the part of many of the commercial firms; and, at the suggestion of the Secretary, we have cut down the meetings for 1949 to the Annual Meeting at San Francisco and an Areal Meeting at Atlanta.

Since there has been so little demand for its services, it seems to the Secretary that we should do away with the Committee on Post-War Courses in Pediatrics and return the balance of the fund which Mead Johnson and Company so generously placed at our disposal. Dr. McQuarrie, Chairman of the Committee, concurs in this suggestion.

We must, however, begin again to think of reinstituting the Latin-American Scholarships.

We are sorry to report to you the following deaths.

Dr. George M. Cultra, Amarillo, Texas.
Dr. Samuel McC. Hamill, Philadelphia, Pa.
Dr. Marvin Israel, Buffalo, N.Y.
Dr. Gilbert Osincup, Orlando, Fla.
Dr. Oscar Reiss, Beverly Hills, Calif.
Dr. John F. Sinclair, Philadelphia, Pa.
Dr. Talbot A. Tumbleson, Beaumont, Texas.
Dr. Alfred M. Wise, Brooklyn, N.Y.
Dr. Albert H. Montgomery, Chicago, Ill., Associate Fellow.
Dr. Noel C. Womack, Pocahantas, Miss., Emeritus Fellow.

Respectfully submitted,
CLIFFORD G. GRULEE
SECRETARY

It was moved, seconded and carried that the Secretary be authorized to re-establish the Latin American Scholarships.

The report of the Secretary was accepted.

REPORT OF THE TREASURER

Statement of Receipts and Disbursements, July 1, 1947 to May 31, 1948

Balance in checking a/c—July 1, 1947		$ 11,920.07
Balance in savings a/c—State Bank & Trust Company		13,371.07
Balance in savings a/c—First National Bank & Trust Company		8,321.29
		$ 33,612.43
Receipts:		
Dues	$41,539.50	
Exhibits—Salt Lake City, Sept. 1947	250.00	
Dallas, Dec. 1947	8,975.00	
Buffalo, Apr.-May 1948	5,390.00	
Milwaukee, June 1948	2,477.50	
1st Pan-American Congress, Cash taken in	1,998.00	
Areal Meeting, SLC, cash taken in	1,449.50	
Annual Meeting, Dallas—Allergy Seminar	550.00	
Blood Seminar	612.50	
Registration	7,079.50	
Round Tables	2,165.00	
Areal Meeting, Buffalo—Registration	3,617.50	
Clinic	465.00	
Areal Meeting, Milwaukee—Registration	876.25	
Initiation Fees	6,725.03	
Interest Earned	702.23	
Pamphlets—Child Health Record	$ 743.37	
Immunization Procedures	843.99	1,587.36
Committee—Improvement Child Health	27,878.90	
Amount received from Region IV with interest	809.56	
PEDIATRICS	11,330.00	126,478.33
		$160,090.76
Disbursements:		
Annual Meeting—Pittsburgh, Feb. 1947	64.63	
Areal Meeting—SLC, Sept. 1947	2,954.07	
Annual Meeting—Dallas, Dec. 1947	18,088.41	
Areal Meeting—Buffalo, Apr.-May, 1948	4,181.68	
Areal Meeting—Milwaukee, June, 1948	600.34	
Areal Meeting—Seattle, Sept. 1948	55.91	
Annual Meeting—Atlantic City, Nov. 1948	5.39	
Bank Charge and Exchange	52.34	
Certificate Expense	122.68	
Executive Board	7,877.41	
Miscellaneous	402.27	
Office supplies & Equipment	445.40	
1st Pan-American Congress	12,484.22	
PEDIATRICS	10,784.50	
PEDIATRICS—Special Account	3,077.76	
Postage	1,053.91	
Rent	2,503.53	
Salaries—Secretary	14,666.67	
Assistant Secretary	2,750.00	
Office	6,861.34	24,278.01

Stationery & Printing		2,946.90	
Telephone & Telegrams		599.12	
Travel—Secretary		1,196.31	
Treasurer's Bond		342.50	
Expense—Districts	491.97		
States	215.91		
Committees	10,907.62	11,615.50	
Pamphlets—Child Health Record	969.19		
Immunization Procedures	1,808.83	2,778.02	
International Congress Assessment		520.00	
Transferred from savings a/c to ICH Committee		5,000.00	
Transferred from Research on Child Development to ICH Committee		59.00	114,089.81
Balance—May 31, 1948			$ 46,000.95
Balance in checking a/c—May 31, 1948			21,726.77
Balance in savings a/c—State Bank & Trust Company			15,143.33
Balance in savings a/c—First National Bank & Trust Company			9,130.85
			$ 46,000.95

Report was accepted.

REPORT OF DISTRICT I

On April 22, 1948, Dr. Harold J. Root, State Chairman for Connecticut, called a meeting of the fellows of Connecticut for the purpose of organizing and adopting a constitution and by-laws; also to discuss the action of the Executive Board on February 8, regarding pediatric education. Drs. Sisson and Snedeker of Boston were present at this meeting.

On May 19, Dr. James M. Baty, State Chairman for Massachusetts, called a similar meeting of the fellows of that state for the same purpose.

The result of these two meetings was the adoption of state constitutions and by-laws very similar in character, differing only to meet certain contingencies in the respective states. The main features of their constitutions are as follows: The president of the organization will be the State Chairman, the vice-president, secretary and treasurer and two other members elected at large constitute the Executive Committee. Their duties are to discuss and make recommendations pertaining to any of the activities of the Academy. An annual meeting will be held one month prior to the Annual Meeting of the Academy at which time the activities of the Executive Committee will be acted upon.

Dr. Sisson explained to the Connecticut fellows the background and facts pertaining to the action of the Executive Board suggesting federal aid for pediatric education. Following this they voted unanimously favoring the action of the Executive Board.

Dr. Baty presented two questions to the fellows of Massachusetts for their action as follows: (1) Are you in favor of the general principles on pediatric education as presented by the ICH Committee? They voted 44 favorable—2 abstaining. (2) Are you in favor of requesting federal funds to assist in pediatric education? The vote was as follows: Yes—18, No—10, 18—abstaining.

Respectfully submitted,

OLIVER L. STRINGFIELD, *Chairman*

REPORT OF DISTRICT II

The major activity of District II was the Areal Meeting in Buffalo. This meeting was a great success and is a tribute to Dr. Orr, State Chairman. An excellent scientific program was arranged by Dr. Rubin, Chairman of the Program Committee. The program was augmented by scientific exhibits illustrating central nervous system disorders such as, cerebral birth injuries, subdural hematoma, epilepsy, encephalitis, mental deficiency, intracranial tumors.

The total attendance was about 1100. Approximately 500 members attended.

The first report of the Study of the Child Health Services in New York State was presented by Dr. Wheatley in Buffalo before representatives of the State Health Department, the pediatric representatives of 12 districts of the New York Medical Society, the Child Welfare Committee of the New York State Medical Society, and the Study Committee of the American Academy of Pediatrics. This report was also given subsequently at the meeting of the Medical Society of the State of New York in New York City on May 20 by Dr. Wheatley. This was a preliminary report covering the activities of practitioners only. However, it contained many items of particular interest. It uncovered the fact that in this predominantly urban state approximately three-quarters of the children are patients of general practitioners. This is true even in New York City. Also there are twice as many pediatricians per capita in the metropolitan district as there are in the upper part of the state. The great significance of this is that we have at one and the same time released the report to the official agencies, to the State Medical Society, and to the Academy membership.

Another important activity was the introduction of a resolution into the House of Delegates of the State Society of New York at its Annual convention in New York in May asking the approval of the recommendation of the ICH Committee that federal funds be sought to improve pediatric education. This resolution was introduced by Dr. Orr. It was referred to the Reference Committee on Child Welfare, which has as its chairman Dr. Givan. Although there was considerable discussion within the Reference Committee, they recommended unanimously its adoption. On the floor of the House of Delegates Dr. John Hubbard was asked by the Speaker of the House to appear and make a statement regarding the resolution presented by Dr. Orr. After considerable discussion a motion was carried that the resolution be referred to the Council of the New York State Medical Society for their action. Personal opinions that have been expressed by members of that Council would lead one to be optimistic of its final adoption.

It is encouraging to note that there were 33 applications for fellowship in the Academy from District II since the last regular meeting of the Executive Board.

Respectfully submitted,

PAUL BEAVEN, *Chairman*

REPORT OF DISTRICT III

There has been considerable discussion of the action of the Executive Board regarding the proposal of the ICH Committee. With no complete poll, New Jersey seems to be in the main opposed to this action. Delaware and Pennsylvania have a majority in favor of the proposal.

The Academy in Pennsylvania was instrumental in activating a refresher course in pediatrics given in two sections, one in Philadelphia under the auspices of the University of Pennsylvania and one in Pittsburgh under the auspices of the Medical School there. This was financed by the State Department of Health.

The Academy fellows in Delaware are planning a similar course to be instituted this year in conjection with the county societies.

New Jersey already has well attended refresher courses.

Respectfully submitted,

PHILIP S. BARBA, *Chairman*

REPORT OF DISTRICT IV

The activities of District Four have been principally concerned with the Academy Study and the preparation of reports. All of the states have received their return from the Study and are in the process of preparing their final report. The North Carolina Report has been completed and published.

Fellows in District Four are happy that Atlanta has been selected as the place for the next Areal Meeting and extend to all fellows of the Academy a cordial invitation to attend.

Respectfully submitted,

ARTHUR H. LONDON, JR., *Chairman*

REPORT OF DISTRICT V

In Ohio the Committee on Fetus and Newborn is cooperating with the Children's division of the State Health Department in carrying out the provision of its sanitary code as it pertains to maternity hospitals and nurseries. The Committee also offered its support and cooperation in a contemplated premature program. It asked the director to look with favor on the rooming-in plan for maternity hospitals.

In Kentucky the post graduate course in pediatrics at the Louisville Children's Hospital has been given again with great enthusiasm on the part of the participants. This course is given once a week for eight weeks and lasts three hours each session. With this arrangement men come from within a radius of one hundred miles and it does not interfere seriously with their practice.

Uppermost in the minds of all at the present time is the question of requesting government aid for medical education and for pediatrics in particular. Opinions differ so much that it would be impossible to express them adequately in a report of this kind.

Respectfully submitted,

JAMES W. BRUCE, *Chairman*

REPORT OF DISTRICT VI

All State Chairmen of District VI but one reported that in their opinion a majority of the pediatricians in their respective states are in favor of federal aid for pediatric education.

State reports of specific Academy activities were received from two State Chairmen.

Their reports follow in their original form. Dr. Poncher's report is a summation of many activities now under way in Illinois, in whose initiation and organization he has played an active part.

This is Dr. Poncher's final report as he has now been succeeded by Dr. Eugene T. McEnery.

Respectfully submitted,

GEORGE F. MUNNS, *Chairman*

Dr. Munns read extensive reports from Dr. H. G. Poncher, past State Chairman of Illinois and Dr. R. E. Nutting, State Chairman of Minnesota.

REPORT OF DISTRICT VII

The primary work has been to straighten out the recommendation of the ICH Committee. Missouri was not definitely opposed to the proposition, Texas is very much so, and Mississippi and Alabama are not in favor of it. In Texas most of the agitation has quieted down because fellows know the matter is going to come up at the Annual Meeting.

We have had refresher courses which were well attended. In Louisiana the Hogg Foundation has been doing a great deal toward mental health. Representatives are participating in a meeting in London. The group studying at the University of Texas has been asked to act as a commission. A letter from Maud W. Keeling, Secretary of the Hogg Foundation reads as follows:

> Dear Dr. McElhenny:
>
> I thought you might like to know just how far and wide your wisdom is traveling. Inasmuch as we did not organize as a Preliminary Commission or meet with that purpose in mind, I think it is quite a compliment to the group to be asked to be considered as a Commission and to send their report to the Program Secretary in London. Thank you again for your help.
>
> Cordially,
>
> (Signed) Maud W. Keeling

Respectfully submitted,

THOMAS J. MCELHENNY, *Chairman*

REPORT OF DISTRICT VIII

The plans for the western areal meeting to be held in Seattle, September 13, 14 and 15 are well under way. The Committee on Arrangements has planned for entertainment preceding the meeting.

The state reports on the Study of Child Health Services are going forward in most of the states. One state in particular, Oregon, has had a representative from the central office write its report. Other states intend to make their local interpretation along different lines. We are hopeful that the vast amount of material may be used to advantage.

Since the last Executive Board meeting we have not had much discussion regarding pediatric education. Opinion in District VIII is still quite divided as to the proper method of helping medical education.

Respectfully submitted,

V. W. SPICKARD, *Chairman*

REPORT OF DISTRICT IX

All branches of District IX have worked with great enthusiasm to improve the development of the pediatric sciences in Latin America under the auspices of the Academy.

The Annual Meeting of the Cuban Branch in Camagüey City offered an opportunity for a general reunion of the Cuban Pediatric Society with attendance of representatives from Yucatan, Merida, and Mexico City.

All fellows of District IX have received with pleasure the new journal of the Academy, PEDIATRICS, and express their satisfaction with the Spanish abstracts accompanying all original papers.

The program to be presented at an evening session of the Annual Meeting of the Academy in Atlantic City has been organized with Mexico, Guatemala and Cuba, contributing. An effort is being made to stimulate attendance of Latin American members at the Annual Meeting.

The District Chairman will attend a meeting of the special committee in Mexico City for the organization of the second general reunion of Districts IX and the Second Pan-American Pediatric Congress, which will be held in Mexico during the first week of November 1949. This will be an opportunity to discuss with the fellows of Mexico the agenda of these events. We request now any suggestions which members of the Executive Board may have for the Program Committee of the Congress.

We would appreciate some action of the Executive Board to stimulate the publication of the proceedings of the Pan-American Pediatric Congress.

Respectfully submitted,

FÉLIX HURTADO, *Chairman*

REPORT OF THE COMMITTEE TO CONFER WITH THE TRUSTEES OF THE A.M.A.

The Committee consisting of Drs. Sisson, Beaven, Garrison, Thelander, Hubbard, Conklin and Webb had a conference with the Trustees of the American Medical Association with repect to the proposed legislation for support of pediatric education. The Trustees passed the following resolution:

"The Council has gone on record favoring an intensive effort to secure voluntary support for medical education. Therefore, the Council is opposed to the plan of the American Academy of Pediatrics. The Council feels that it is extremely unwise for one specialty in medicine to seek federal support before medicine and medical education in general have approved this principle."

Extensive discussion was carried on by various members of the Committee, especially Dr. Beaven and Dr. Sisson.

The Committee was thanked but no definite action was taken by the Executive Board.

Respectfully submitted,

WARREN R. SISSON, *Chairman*

Report accepted.

REPORT OF THE STUDY OF CHILD HEALTH SERVICES

It is with justifiable pride that your Committee is able to report that the formidable assignment you gave us over two years ago is now virtually done.

The collection of the desired information is complete from all states, the District of Columbia and Hawaii. Approximately 6,000 hospitals have been surveyed, mostly by personal visits; two-thirds of all physicians and dentists in private practice have responded to questionnaires; a county-by-county inventory has been made of the services rendered to children by community health agencies. Pediatric education has been carefully evaluated by personal visits to the approved medical schools and hospitals accredited for residency training in pediatrics. A supplementary survey was done in four selected states so that data obtained by interviews rather than mail questionnaires could be used to check the validity of the basic statistical methods.

The analysis of the massive data could well occupy a statistical staff for several years. We have endeavored to draw off the cream and produce a report while the information is still fresh and cogent.

National Report

Preliminary draft of an overall national report is now nearing completion. We propose to publish the report in four parts of separate volumes as follows:

I. A summary of the most important findings of health services for children in the United States.

II. A review of pediatric education based upon personal visits to the approved medical schools and the hospitals approved for pediatric residency.

III. A compilation of detailed statistical tabulations which will constitute an appendix for Volume I.

IV. A collection of reprints of articles which describe special features of the Study.

State Reports

While at the national level an overall summary has been prepared, more detailed reports are being written in the individual states under the direction of State Chairmen. We anticipate that these state reports, including detail at county and local levels and including also recommendations made by duly appointed state committees, will collectively represent one of the most valuable—if not the most valuable—results of the study.

The report of the Child Health Services in North Carolina, our pilot state, has appeared as a supplement to the North Carolina Medical Journal. Approximately 4,000 copies of this report have been distributed. In addition to the normal circulation of the state Journal, copies have been sent to the officers and Executive Board of the Academy, all state chairmen, and a considerable list of others with special interest in the study. State chairmen have received additional copies so that they would be able to submit this material to the medical societies and health departments of their own states.

A descriptive pamphlet, based on the North Carolina report, has been prepared in popular format. This pamphlet has been distributed to all members of the Academy and to a long list of organizations and individuals concerned with the health of children.

Financial Status

We wish to remind you of four points which we have previously reported:

1. In the report submitted to the Executive Board at the Annual Meeting in November 1946, we reported a budgetary deficit of $41,350, needed to meet necessary expenses during the second year of the study. Of this amount, $10,000 was met by additional contributions, leaving a deficit of $31,350 needed to complete the study.

2. In the second payment of the grant received from the National Institute of Health, we sustained a cut along with all other grantees of 15%, or $18,150.

3. Owing to the work involved in preparation of the material presented at the Annual Meeting in Dallas and owing also to the unexpected difficulties encountered in completing the analysis of community health agencies, our operating schedule was delayed by two to three months. Accordingly, salaries for the statistical staff—the heaviest item—exceeded our carefully planned budget.

Despite these difficulties, we have managed to meet all expenses up to July 1, 1948, the anticipated date for termination of the study. Furthermore, if our grant from the NIH had not been cut $18,150, and if the states had returned the loans made to them—a total of $24,530—we would now have a balance of $42,680 to complete the study and pay for the cost of publishing the national

report; and, I might add we would have been able to refund to the Treasury of the Academy the $18,000 withdrawn from reserve funds.

After the date of July 1, 1948, we will still have the most important job of transforming manuscript of the national report into final publication. We regret to have to report that for this final essential task the funds are not in hand.

Anticipating that additional financial assistance would be needed for the publication of the report, the Chairman and the Director of your Committee together with Dr. Wilson called upon the Commonwealth Fund to explore the possibilities of having the Commonwealth Fund publish our report. In these preliminary discussions we gained the distinct impression that the Commonwealth Fund would give favorable consideration to a request from the Academy to have their editorial department undertake this publication. In view of the financial considerations which have been reported above, it is now requested that the Executive Board authorize the Chairman of your Committee to make a formal request to the Commonwealth Fund.

In the event that the Commonwealth Fund will undertake the publication of the report there will still remain the necessity of meeting the cost of typing, final checking of all the statistical material and the drafting of some 150 charts which we have prepared in preliminary form. Based upon these considerations we have estimated that the minimum amount necessary to finish the study and complete the report will be approximately $8,841.00 after expenses are paid on July 1.

Respectfully submitted,

WARREN R. SISSON, *Chairman*
JOHN P. HUBBARD, *Director*

REPORT OF THE COMMITTEE FOR IMPROVEMENT OF CHILD HEALTH

Since recommendations of the Committee for Improvement of Child Health have been reported fully in recent meetings of the Executive Board, this report is limited to only two items, which although they represent much time and effort can be stated very briefly.

First, at the special, called meeting of the Executive Board in Buffalo April 29, you requested the Committee for Improvement of Child Health together with the Committee on Legislation "to conduct through PEDIATRICS and other channels an informative and factual exposition of the exact reason for the recommendation for federal aid to pediatric education." In keeping with this request, active measures have been in Progress from the central office of the Committee. The North Carolina Report has been used as the means of introducing the program of the Academy to state medical societies, editorial writers and others whom it has been deemed advisable to contact. This distribution provided an opportunity to describe the objectives of the Academy as expressed in the recommendation of this Committee. Approximately 4,000 copies of the report, which appeared as a supplement in the North Carolina Medical Journal have been distributed.

A list of the House of Delegates of the American Medical Association has been mailed to all state chairmen in order that the state chairmen might inform as many delegates as possible of the reasons for the recommendation of your Committee.

The article on "Health Services for the Rural Child" which appeared in the May 22 issue of the J.A.M.A. has been reprinted with appended tables which list child population and number of beds, physicians, and dentists, county by county, throughout the entire United States. Reprints of this article have had wide demand from many sources and have had broad circulation as another means of informing both professional and non-professional groups of the study and the continuing program of the ICH Committee.

Another pamphlet somewhat similar in format to the popular version of the North Carolina report is being prepared. This pamphlet, under the provisional heading, "The Road Ahead for Better Child Health," attempts to portray the findings of the Study, the need for better distribution of medical care and the program which has been recommended to bring better care to children, especially in rural areas.

Secondly, the staff of the Committee for Improvement of Child Health has been endeavoring to give active support to the Ways and Means Committee in raising funds for the proposed budget. In this connection we have made personal contact with a long and time consuming list of foundations, funds, commercial houses and individuals.

As a direct result of these efforts we are happy to report that we have succeeded in raising $36,328.90 in cash and commitments to date, which are being turned over to the Treasurer as checks are received. Cultivation through mailings of literature is in progress with additional prospects.

In addition to these foundations and commercial houses, efforts have been made to assist and encourage state chairmen to seek funds from sources with which they have personal contact.

Respectfully submitted,

JAMES L. WILSON, *Chairman*
JOHN P. HUBBARD, *Director*

The reports of the Committee on the Study of Child Health Services and the Committee for Improvement of Child Health were considered together.

It was moved, seconded and carried that the Study Committee be empowered to use funds up to $3,000 donated by the Academy for the Committee for Improvement of Child Health to meet the deficit of the Study and that the money accruing from the states for funds advanced by the Study Committee be used to reimburse the funds of the ICH Committee so appropriated. If the amount collected from the states should exceed $3,000, the balance is to go to the reserve fund of the Academy.

REPORT OF THE COMMITTEE ON LEGISLATION

It is particularly desirable to report the sentiment of the Committee relative to the status to date of the proposed legislation for federal support of pediatric education. For your information, pertinent events are as follows:

1. At a meeting in Chicago in February the Executive Board approved in principle the recommendation of the ICH Committee.

2. Dr. Hubbard, following conferences with your Chairman and Dr. Wall, testified on the School Health Services Bill before the Senate sub-committee on Labor and Public Welfare. This testimony presented statistics from the Academy's Study, establishing the need for more doctors trained in child care. It was emphasized that funds should be made available to support the training of physicians before any attempt to improve child health could be effective.

3. At a meeting in Buffalo in April the Executive Board confirmed its previous action (see resolution attached) and expressed the opinion that steps should be taken to inform appropriate authorities of the AMA of the activities and objectives of the Academy. A committee consisting of Drs. Sisson, Beaven and Munns was appointed for this purpose. It was learned in informal discussion with AMA authorities that the House of Delegates was the proper approach rather than the Board of Trustees.

4. On April 30 Senator Thomas of Utah introduced S. 2588 "to provide grants and scholarships for medical education and grants for dental, nursing and public health and for other purposes"—an all inclusive federal aid program for medical education, which would of course include support for pediatric education.

5. At a meeting of the New York State Medical Society in May, Dr. Orr introduced a resolution in the House of Delegates asking approval of the recommendation approved by the Executive Board in support of federal funds for teaching in the field of medical care for children. The resolution was approved by the Reference Committee and has been referred to the Council.

6. After much thought on the matter it seems best not to attempt to have a resulution approved in the House of Delegates of the AMA in June. It is considered wiser to allow more time during which AMA delegates can be properly informed before official AMA action is requested.

It is recommended that the following informative material should be read: (1) March PEDIATRICS, pages 387-391; (2) A Further Statement on Federal Aid for Pediatric Education, recently distributed to the Academy membership by Dr. Grulee; (3) March-April issue of "Progress Pediatric Study"; (4) JAMA May 8, pages 187-188, report of Council on Medical Education and Hospitals, item page 212 "Situation from Viewpoint of Psychiatrists."

Respectfully submitted,

COURSEN B. CONKLIN, *Chairman*

Report accepted.

REPORT OF THE COMMITTEE INVESTIGATING SECTIONS AND AFFILIATE MEMBERSHIP IN THE ACADEMY

Allergy: The following group will act as a steering committee for the Section on Allergy, which will include not only this committee, but the members of the Academy of Pediatrics who have been certified by the American Board of Pediatrics Subsection on Allergy, (there are at present 32 such members): Drs. William P. Buffum, William C. Deamer, Jerome Glaser, Lewis Webb Hill, W. Ambrose McGee, and Bert Ratner, Chairman.

Two seminars are to be given at the Atlantic City Meeting, one by Dr. Ratner, the other by Dr. Hill, each being aided by other members of the committee.

There has been a diversion created by some other pediatric allergists who feel that there should be, in connection with the Academy meetings, a program on allergy to which all who are interested in allergy would be invited, whether they be members of the Academy or not. Such a group has already been organized. The attitude that Dr. Ratner and Dr. Hill have taken is that anyone can do what he pleases, but what they are interested in is to bind together those who are diplomates in pediatric allergy. These diplomates are all members of the Academy, and no one outside the Academy will be asked to become a member of the section. It is clear from correspondence among the different allergists that what we have started will be stable and that what was proposed and could have been disruptive will not materialize.

Mental Growth and Development: At a meeting in New York attended by Drs. Langford, Senn, Bakwin, Levine, Ratner, and myself the evolution of this part of the Academy program was discussed. We all thought there would be a great deal of value in proceeding in a pattern outlined by the group on allergy. There would be a steering committee of Academy members who are specialists in growth and development. There would also be a section of members of the Academy who are clearly outstanding students in that field. As yet there is no such thing as a board of pediatric psychiatry or any equivalent name, so that part of the pattern could not be followed. In general, however, it would be the same.

The question of nomenclature was discussed at length, and it was unanimously agreed that "Mental Growth" or "Mental Growth and Development" would be the name to give to this section.

Also following the pattern of the allergy group, it was decided that the head of this section would be the present chairman of the Academy Committee on Mental Health, Dr. Senn. He, in turn, would appoint a committee of five more members and those six would determine the eligibility of any Academy member who would be asked to be in this group. This cannot be accomplished until the November meeting, since the members of the present committee on Mental Health hold their positions until that time.

Surgery: This group would differ from the other two in that they would not be fellows of the Academy. They would be elected by vote as Affiliate Fellows of the Academy, nor would they necessarily be diplomates of the American Board of Surgery.

As in the other two sections, there would be a group chosen for this section. They would also have a steering committee, the head of which would be the one who has had the most to do with the formation of this section, Dr. Coe. He could choose five other men to act with him. He has suggested the names of surgeons who might meet and determine the eligibility of others for the section. Those men could, then, meet at Atlantic City and review the situation as outlined.

Comments: There has been considerable discussion in the Committee regarding the word "Section" as being an appropriate one. It has been suggested that it will appear to simulate the sections in the A.M.A. This, however, is not necessarily true, since nearly all medical academies have sections within their membership and it would not connote the construction of the A.M.A. any more than it would the construction of any other academy. We therefore, recommend that the groups be designated as sections.

Another suggestion that was not discussed but has been made is that there was no point in speaking of pediatric allergists or pediatric surgeons, etc., since if they are members of the Academy of Pediatrics, they are by that fact pediatricians. That could be decided easily by the Executive Board.

All three of these sections would be patterned in the same way. When they are successful and demonstrate their value, then the time would arrive, it seems to us, to consider other sections; such as, roentgenologists, pathologists, etc. That time has not yet arrived.

A matter that should be seriously considered is the rotation of the committee. While the mem-

bership of a section naturally would be permanent, the committee itself should be of limited tenure. It might be well to have the chairman serve for three years and the six members elected two each year for a period of three years. At the first appointment they could be staggered, being appointed for one, two or three years.

The value of this venture to the Academy will be dependent in no small measure on the cooperation of the sections in the programs with which they would be naturally in consultation with Dr. Martmer. Of equal importance, however, would be the value of this group to the men themselves. A small group of allergists or a small group of those interested in mental development or those interested in surgery could well use this as an outlet for discussion of subjects of vital interest to them but of no particular interest to pediatricians in general. Such meetings could be held just prior to the regular Annual Meeting of the Academy.

Discussions have been held as to the best method of classifying the members of the sections within the directory. The consensus of this committee is that the names of the affiliate members would be listed in the regular Academy membership, and these names would be followed by a symbol indicating that they are affiliates in surgery. The members of the sections on allergy and on mental growth, since they are members of the Academy, would appear as previously in the body of the directory and they also would have a symbol for the section to which they belong. In an appropriate place in the directory the members of each section, together with its steering committee, could be listed as a group.

Respectfully submitted,

HERBERT E. COE, M.D.
BRET RATNER, M.D.
PAUL W. BEAVEN, M.D.

It was moved, seconded and carried that Dr. Coe ask a group, not to exceed 20, who are practicing only pediatric surgery to form an affiliate group of surgeons.

It was moved, seconded and carried that the word "Section" as it appears in this report be approved.

It was moved, seconded and carried that the application blank for affiliate membership be approved.

It was moved, seconded and carried that the term of office of the Chairman of the Steering Committee be three years and that he can succeed himself for only one term.

Report accepted.

REPORT OF THE COMMITTEE ON CONTACT INFECTIONS

The Committee on Contact Infections considered a report from Dr. J. A. Myers, Chairman of the Tuberculosis Committee of the American School Health Association, suggesting that his Committee and the Committee on Contact Infections of the Academy pool their efforts cooperatively, in the combating of tuberculosis in children. There was general agreement among the previous members of the Committee on Contact Infections as to the advisability of such a cooperative venture, but no formal action had been taken. To motivate this cooperative venture, the Committee on Contact Infections suggested to the Executive Board that the following resolutions be acted upon:

That the Committee on Contact Infections of the American Academy of Pediatrics approve the pooling of our activities with the Committee on Tuberculosis of the American School Health Association.

That the Committee on Contact Infections of the American Academy of Pediatrics approve in principle the certification procedures established by Drs. Myers, Myerding, Slater, and Jordan in the State of Minnesota.

That the Committee on Contact Infections recommend that local representatives among the Academy members be appointed in each state or subdivision of the Academy in the United States. It shall be the purpose of these representatives to establish a working relationship with the local or state tuberculosis association and the educational divisions within the state in an effort to establish tuberculin certification programs in all of the schools within the United States.

Respectfully submitted,

JOHN A. ANDERSON, *Chairman*

Report accepted.

REPORT OF THE COMMITTEE ON COOPERATION WITH NONMEDICAL GROUPS

Our District Committee for Cooperation with Nonmedical Groups is now organized completely and, after consultation with the National Chairman, Dr. James C. Overall, Nashville, Tenn., we are ready to proceed with some of the activities of our committee. The following suggestions have been made:

1. Contact state or province camping group, determine what standards are being used for physical examinations, and see whether they are interested in using the standard card approved by the Academy of Pediatrics. We should like to have them used universally in all camps in your particular area.

2. Contact local state board of health, and determine the standards for camps in your area. Some states have adequate supervision while others are making no efforts along these lines.

3. We should like to contact state P.T.A. Health Chairmen, and acquaint them with the workings of our committee, and our willingness to be of assistance in any way possible. This should include suggestions as to speakers at local meetings, and any other service which might be requested.

4. Contact the state headquarters of the Girl and Boy Scout groups, advising them of the program of our committee, our willingness to suggest speakers, and inquire whether they would be interested in using our physical examination record card.

5. Consider the appointment of local sub-committee members who could assist in the work of this committee. In the larger centers, it would probably be advisable to have several members.

Respectfully submitted,

JOHN E. BROWN, JR., *District V Chairman*

The above is an excerpt from a letter sent to the members of the Committee which was read. No action was taken.

REPORT OF THE COMMITTEE ON SCHOOL HEALTH

In the special report of this Committee (see April PEDIATRICS) we described briefly two serious controversies concerning school health programs, and called attention to a series of principles (see Public Health, Nursing and Medical Social Work Section of PEDIATRICS for April) which aimed to avoid the futility of conflict and to provide a basis for agreement. The hearings of the School Health Services Bill before the health subcommittees of the Senate Committee on Labor and Public Welfare on March 8 and 9 brought out the absurdity of the rivalry over the jurisdiction to such an extent that the issue of free medical care regardless of ability to pay practically disappeared as a cause for conflict. Both the testimony of Dr. Vlado A. Getting for the State and Territorial Health Officers and Dr. Reginald M. Atwater for the Executive Board of the American Public Health Association emphasized the state health agency as the single responsible agency for administration while the State Commissioner of Education (Irwin) from North Carolina representing the National Council of Chief State School Officers appeared even more insistent that the administration must be under the control of the state education departments.

This irrational rivalry for jurisdiction seems all the more absurd when we consider that the Association of State and Territorial Health Officers passed a resolution on April 12, 1945 approving that "school health programs be recognized as a joint responsibility between the health and education departments on federal, state and local levels" and the Section Council of the School Health Section of the American Public Health Association had unanimously approved of the series of principles already mentioned with a similar emphasis upon joint planning and responsibility. As many state school executives have recognized the contribution made by the medical and public health professions and have gone beyond joint planning even to accepting medical and public health leadership for many aspects of the school health program, it is obvious that the testimony of all the state school executives was not represented by Mr. Irwin.

The significance of this perverse turn of affairs in the evolution of school health programs is not clearly apparent, but it does seem obvious that considerable thought and effort will be necessary from the Academy, from all medical societies, from educators and from the public health groups,

before we can avoid quarreling and bring all the professional resources of the community into an improved educational and advisory service program for the benefit of the school child. The issue of "Federal funds to provide treatment for those who are able to take care of themselves" is only part of the problem, and it will assume much less importance as those who have been raising this issue come to more understanding of the tremendous implications and possibilities of health education, physical education, case finding, follow up and guidance in the use of community medical facilities.

There has been developed a great deal of agreement upon school health policies, but the war over jurisdiction and over free treatment services for all those who are able to employ their own physician has held back the development so much needed. Apparently the problem has become involved in public health circles with the resolution of the American Public Health Association, (Statement on Medical Care in a National Health Program, American Journal of Public Health, December 1944.) As this seems to be a closed chapter, the emphasis upon a single agency administrative responsibility appears as a policy in conflict with the necessity for joint planning and decisions as to who will do what.

It has long been obvious to Academy leaders that health and education departments must develop more team work in the school health program. When Academy members participate in bringing this about, they create new fields of public relations which are so essential for a proper safeguarding of private practice. Joint planning at the local and state level is a particular opportunity for Academy members to share in program development with educators and public health officials. Such opportunities are one of our greatest assets in developing confidence, understanding and improved public relations. If Academy leaders will share in the developing plans for rheumatic fever consultation, for hard of hearing, orthopedic and mental health consultation services, they can offer the guidance so necessary for new programs. To plan for the facilities for treatment of those who are not able to employ their own physician is certainly the prerogative and duty of practicing physicians. Constructive Academy leadership in these changing phases of child health can be most effective through active participation in problem solving with education and health officials.

Respectfully submitted,

HAROLD H. MITCHELL, *Chairman*

Report accepted.

It was moved, seconded and carried that Dr. Stringfield be asked to write to Dr. Mitchell asking him to prepare a bill on the order of S-1290.

REPORT OF THE COMMITTEE ON COOPERATION WITH GOVERNMENT AND MEDICAL AGENCIES

A meeting of the Committee and invited consultants was held on April 29 at Buffalo. Present were Drs. John A. Toomey, Warren R. Sisson, Clifford G. Grulee, Paul W. Beaven, Albert D. Kaiser, Marshall C. Pease, Margaret M. Nicholson, Joseph I. Linde, Joseph S. Wall, Frank Van Schoick, James C. Overall, and Vernon W. Spickard.

Three major points were agreed upon by the majority present to promote the cooperation of governmental and medical agencies:

(1) Creation of a National Child Health Conference on child health matters of the four chief governmental and medical agencies (A.M.A., A.A.P., U.S.P.H.S., U.S. Children's Bureau).

(2) Creation of a united front by the Academy, the American Medical Association and state medical societies as to the "restriction of the use of public funds to those groups of the population unable to pay for medical services," regarding provisions for maternal and child welfare.

(3) Pursuant to an agreement of the Academy and the American Medical Association as to this "means test," the National Child Health Conference of governmental and medical agencies select as an "area of agreement" the vital "problem of providing better pediatric medical care for children in low income families" and promote voluntary plans along that line.

Recommendations to the Executive Board by the Chairman of this Committee are as follows:

1. In view of the present urgent situation, it is strongly recommended that the American Academy of Pediatrics, at this time, sponsor a National Child Health Conference, meeting regularly, to be composed of the chief federal and medical agencies working in the child health field—to aid in the

formulation and coordination of the child health activities and programs of the federal governmental agencies and correlate them with the child health activities of the American Medical Association and the American Academy of Pediatrics in such "areas of agreement" as may be discovered by the Conference.

2. It is recommended that the National Child Health Conference (recommended) be urged to select an "area of agreement" as a primary objective and to work together to solve this most urgent problem of providing good quality pediatric medical care for children in low income families.

Respectfully submitted,

STANLEY NICHOLS, *Chairman*

It was moved, seconded and carried that this Committee be discontinued.

REPORT OF THE COMMITTEE ON FETUS AND NEWBORN

Members of the Committee on Fetus and Newborn are working on a revision of the manual for newborn care which will be ready before the next Annual Meeting.

State Committees on Fetus and Newborn have been appointed in every state but one, in four Canadian Provinces and in Hawaii. In a number of states these committees are active. These state committees have been provided with a tentative program and suggestions for improving the care of newborn infants.

Respectfully submitted,

STEWART H. CLIFFORD, *Chairman*

Report accepted.

It was moved, seconded and carried that Dr. Stewart H. Clifford be empowered to approach one of the commercial firms to see if they would be willing to print the manual and that the Secretary be empowered to authorize this if the request were granted.

REPORT OF COMMITTEE ON HOSPITALS AND DISPENSARIES

Recognizing the closeness of this Committee to the Committee for Improvement of Child Health, we have discussed with Dr. Hubbard this interrelationship.

The following should be pertinent study problems for this Committee in the future:

1. The availability of schooling for hospitalized children.
2. Standards of several play materials for hospitalized children.
3. The extent of freedom which can be properly and safely allowed children in hospital wards.
4. The development of a consciousness in hospital personnel of growth and development in the parade of children through hospitals and clinics.
5. The ratio of nurses, internes, assistant residents and residents to the number of patients in the establishment of some set standard.

The members of the Committee have discussed these various points by correspondence, and the Committee will meet possibly at the Annual Meeting and develop them in more concrete form.

Respectfully submitted,

PETER G. DANIS, *Chairman*

Report accepted.

REPORT OF THE COMMITTEE ON MEDICAL EDUCATION

The Committee on Medical Education deferred its report pending the formal publication of the report on the survey by Drs. Hubbard and Mitchell.

Respectfully,

JOSEPH A. JOHNSTON, *Chairman*

It was moved, seconded and carried that the Committee on Education be asked to take the report of the Study Committee in relation to pediatric education, study it carefully, and formulate recommendations for presentation to the Executive Board.

REPORT OF THE COMMITTEE ON MENTAL HEALTH

No formal report was made. As to the film, "Problem Child," on the request for a ruling by Pet Milk Company, it was voted that the statement, "No prints of films are to be sold to health departments or other groups of individuals," be abolished. It was moved, seconded and carried that the method of distributing the film, "Problem Child," be approved. It was moved, seconded, and carried that the film can be shown to any interested persons.

Respectfully submitted

MILTON J. E. SENN, *Chairman*

RESOLUTIONS PRESENTED BY THE COMMITTEE FOR IMPROVEMENT OF CHILD HEALTH

The Committee appointed to revise the resolutions presented by the ICH Committee presented a report as follows:

Whereas, it was announced before the House of Delegates of the American Medical Association at its annual meeting in Chicago in June 23, 1948, that the Board of Trustees has approved a recommendation of the Council on Medical Education and Hospitals to establish immediately a national foundation, the purpose of which is to secure contribution from the general public for the support of medical education,

Whereas, this action on the part of the American Medical Association is an effort to meet the financial needs of medical education and should accomplish the same ultimate objectives regarding medical education as contained in the recommendation of the Committee for Improvement of Child Health submitted to the Executive Board on February 8, 1948.

Be it therefore resolved that the Executive Board, following a recommendation to this effect by the Committee for Improvement of Child Health, has agreed that attempts to seek federal aid be held in abeyance pending the outcome of the plan proposed by the Council on Medical Education and Hospitals of the American Medical Association, and

Be it further resolved that the American Medical Association be urged to revise its manual on medical education and give due importance to the need for improvement in pediatric education.

Be it further resolved that the Executive Board request the Committee for Improvement of Child Health and the Committee on Medical Education of the American Academy of Pediatrics, to cooperate with the Council on Medical Education and Hospitals of the American Medical Association and make available to the Council information collected during the course of the Academy's study on health services and pediatric education in the United States.

Be it further resolved that a copy of this resolution be sent forthwith to the Board of Trustees of the American Medical Association and be published for the information of the Academy membership.

The Executive Board by vote accepted this interpretation of the I.C.H. resolutions.

The meeting recessed at 8:55 P.M.

The meeting was called to order by the President at 10:30 A.M., Sunday.

REPORT OF THE COMMITTEE ON MOTHER'S MILK BUREAUS

It is obvious that the position of mother's milk bureaus in this country depends very largely upon the degree to which breast feeding in general is practiced. Therefore, we wish to record our appreciation to the Academy for assigning two Round Table Discussions at its Annual Meeting to the general subject of breast feeding. A full discussion by authoritative speakers should be of service to all Academy members, and to the mother's milk bureaus of this country, in clarifying the position at present and improving that in the future.

Respectfully submitted,

CLEMENT A. SMITH, *Chairman*

Report accepted.

REPORT OF THE COMMITTEE ON RHEUMATIC FEVER

Motion picture film on rheumatic fever: The work continues on the script for this film. A revised script has been prepared and has been reviewed again by members of the Committee. This second revision has been sent to the Mead Johnson Company. We are now awaiting their decision regarding the production of the film.

American Council on Rheumatic Fever: There have been no meetings of the Council this year. The American Heart Association, which is the parent organization, has been concerned with reorganization problems and fund raising. It has been felt advisable to give full attention to the parent body this year so that it is on a sound basis. The American Council on Rheumatic Fever received $25,000 from the Paul Whiteman radio contest. Two committees have been named: one concerned with standards of diagnosis, and the other concerned with standards of convalescent care. Neither of these committees has been active so far as your Chairman knows.

Helen Hay Whitney Foundation: The Foundation has been making a survey of rheumatic fever programs throughout the country, particularly those concerned with research projects. It is expected that the Foundation will have valuable information not only on research projects but community programs of care which will be valuable to the American Council on Rheumatic Fever when it becomes an active organization.

Michigan Rheumatic Fever Control Committee: An active and well-organized rheumatic fever program has been developed in Michigan under the sponsorship of the Rheumatic Fever Control Committee of the State Medical Society, with the cooperation of the Michigan Society for Crippled Children and Adults and the Michigan Crippled Children Commission. Started in 1943, it has progressed carefully and slowly until now there are 30 centers for rheumatic fever where specialists give freely of their time to the early detection of the disease. Of these centers, 16 are in major hospitals in Detroit and Wayne county. Dr. Frank Van Schoick, Academy State Chairman, is one of the guiding forces in this program.

Lower East Side Rheumatic Fever Project: For the past year, a rheumatic fever project has been carried on through the Department of Preventive Medicine of New York University College of Medicine, with the sponsorship of the New York Heart Association and the New York City Departments of Health and Education to determine practical administrative methods of detecting and following up children with rheumatic fever and rheumatic heart disease. Your Chairman is a member of the advisory committee and is chairman of the subcommittee on register and procedures. The development of a register has been the chief project this year. It is hoped that experience with the development of a register will lead to a definition of procedures useful to other communities concerned with case-finding and follow-up for rheumatic fever.

At the Committee on Rheumatic Fever meeting in Dallas, the programs of care for rheumatic fever which have been developed by the Children's Bureau and by some other agencies were discussed. It was the recommendation of our Committee that a study should be made of these programs to determine how effectively they are meeting the need. This need for evaluation of rheumatic fever programs is a belief shared by others interested in the problem of rheumatic fever. The programs offer in many instances rather complete schedules of care. They have been in operation—some of them—for nearly ten years. It is important to take stock of them to determine what procedures are effective, to secure knowledge on their cost, to attempt to draw conclusions that may be of value when applied to other programs of medical care.

Consequently, your Chairman feels that the Academy should take the initiative in recognizing that these programs should be evaluated. I would like to have the Executive Board authorize the Chairman to explore ways and means of carrying out such a study. It would be logical for the Academy to request that the Chairman ask the cooperation of the American Council on Rheumatic Fever in this matter, with the possibility that such a study might be carried out as a joint enterprise between an appropriate committee of the Academy and the American Council on Rheumatic Fever.

Respectfully submitted,

GEORGE M. WHEATLEY, *Chairman*

It was moved, seconded and carried that this report be accepted, and that the Chairman be authorized to explore how such a study should be undertaken and to present a program to the Executive Board for its consideration.

REPORT OF THE COMMITTEE ON CARE OF EUROPEAN CHILDREN

Summary of Activities in Connection with Examination of Children at the Reception Center, New York City.

October 1, 1947 to April 30, 1948

I. Children Received 241
II. General Medical Examinations 241
III. Tuberculin Tests 61
(Positive 36)
(Negative 25)
IV. Schick Test 239
(Positive 39)
(Negative 180)
V. Number of X-ray examinations 241
(Hospitalized 7)
VI. Wasserman tests 241
(Positive 1)
(Negative 240)

Age range—Infancy to 20 years—Majority between 15 and 18 years

Nationality of those examined:

Polish	65	Polish-Ukranian	33
Lithuanian	20	Yugoslavian	3
Czechoslovakian	35	Russian	3
Hugarian	19	Austrian	5
Estonian	10	Rumanian	16
Latvian	6	German	4
Stateless	22		

Additional groups of children are still being examined.

Respectfully submitted,

CARL H. SMITH, *Chairman*

Report accepted.

REPORT OF THE COMMITTEE ON PAN-AMERICAN SCHOLARSHIPS

The Secretary was authorized to begin to make arrangements as soon as possible for resuming these scholarships.

REPORT OF THE PROGRAM COMMITTEE

Dr. Martmer reported on the program for Atlantic City.
Report accepted.

REPORT OF THE COMMITTEE ON POST-WAR COURSES IN PEDIATRICS

Since the number of applicants for services along this line has materially decreased in the past months, I would advise that the Committee be dismissed and that the remaining funds left from the grant of Mead Johnson and Company be returned to them.

Respectfully submitted,

CLIFFORD G. GRULEE, M.D.

It was moved, seconded and carried that the Committee be discontinued and that the Secretary be empowered to return the money to Mead Johnson and Company.

REPORT OF COMMITTEE ON TUMOR REGISTRY

A conference of the Committee members in New York was held May 28, 1948.

The members and consultants of the Committee, with one exception, have replied to the inquiries concerning the proposals on (1) a teaching plan, and (2) a committee for the study of radiation effects. All who responded are in favor of the recommendations.

An exhibit of bone tumors in childhood has been prepared and was displayed at the Medical Conventions of the States of New York and New Jersey.

The Committee on Tumor Terminology of the American Society of Clinical Pathologists has requested that a member of the Committee on Tumor Registry of the American Academy of Pediatrics be appointed to serve on their committee. This appointment has been accepted by Dr. Paul E. Steiner.

Additional cases which have been received for registration and consultation since the last report of the Committee was made up are: teratoma, 12-week-old-infant; Wilms' Tumor, 4 years; carcinoma of larynx, 12 years; sarcoma of prostate, 17 months; carcinoma of testis, 14 months; leukemia, 6 years; congenial arterio-venous fistula, 2 weeks; Hand-Schuller-Christian Disease, 3½ months; Hand-Schuller-Christian Disease, 1 year; intra thoracic neuroma, 7 years; rhabdomyosarcoma, lumbar muscles, 7 months.

The resignation of Dr. Herbert F. Jackson was accepted.

The appointment of Dr. Frederick H. Wilke to this Committee is recommended.

Three items are submitted for consideration and action by the Executive Board:

I. *Education:*

1. There has been a considerable demand for small booklets for distribution to physicians and laymen on the subject of childhood cancer. The American Cancer Society is contemplating a distribution to physicians on the entire subject of cancer—including cancer in childhood—on a wide scale. At present the preparation of such a pamphlet for doctors by us would be duplication of this effort and is therefore considered inadvisable.

An article was prepared for laymen, and was published in *Parents' Magazine* in May 1947. Such a brief summary might be presented in pamphlet form with credit given only to the Academy of Pediatrics and the Children's Tumor Registry.

Recommendation: It is recommended that this Committee be authorized to prepare such a pamphlet suitable for laymen. The text and format shall be approved by the Secretary of the Academy prior to any distribution of this pamphlet.

2. The need for broader education in the professional field continues to be evident. A program for teaching has been approved for recommendation to the Executive Board.

Recommendation: It is recommended that the Chairman of this Committee be authorized to transmit to the deans of medical schools, chairmen of state and national societies, etc., the items pertinent to education in childhood cancer, of concern in their particular activities.

II. *Committee for the Study of Radiation Effects:*

The problems arising from irradiation of the child have been a concern of many physicians for some years. This applies not only to the therapeutic use of radium or X-ray but also to the possible effects induced, by cumulative dosage over a period of years, as a result of frequent diagnostic procedures. Furthermore, radio-active isotopes are currently in use of diagnosis and, in some diseases, for therapy. Inasmuch as the effects produced in the mature individual may not parallel those in the growing organism, and since there are very few practitioners who are as familiar with these radiologic agents as they are with most therapeutic and diagnostic modalities used in practice, the members and consultants of this Committee believe that the formulation of some general principles for the guidance of the pediatrician and general practitioner would be a constructive effort in child health.

Recommendation: It is recommended that the Chairman of this Committee be authorized to organize a committee whose objective shall be to prepare a set of general principles for the practitioner as outlined above. This committee shall be composed of the Chairman of the Committee on Tumor Registry, two other fellows of the American Academy of Pediatrics, and two (perhaps one, if more feasible) members of several other national scientific societies. The presidents of the follow-

ing societies shall be invited to appoint one or, if possible, two of their members for this Committee:

American Roentgen Ray Society, American Radium Society, Radiological Society of North America, American Association of Pathologists and Bacteriologists, American Academy of Dermatology and Syphilology, and American Society of Plastic and Reconstruction Surgery.

Respectfully submitted,

HAROLD W. DARGEON, *Chairman*

It was moved, seconded and carried that the Executive Board authorize the preparation of a pamphlet on cancer in children provided that funds are available from the American Cancer Society.

It was moved, seconded and carried that the program the Committee wants to start be approved.

It was moved, seconded and carried that the Chairman of the Committee be authorized to organize a committee whose objective shall be to prepare a set of principles for general practitioners.

* * *

Scientific Exhibits for the Atlantic City Meeting:

Dr. Tom Mitchell was present at the meeting and reported on the efforts to develop Scientific Exhibits for the Atlantic City Meeting.

The National Conference for Cooperation in Health Education:

The Secretary read a letter from Dr. Harold H. Mitchell with respect to the National Conference for Cooperation in Health Education. He recommended that this conference be assured of our interest and desire to participate when more specific plans are developed. It was moved, seconded and carried that Dr. Mitchell's wishes be accorded.

The International Pediatric Association:

Dr. Stringfield reported for the Committee that met with Dr. Holt in regard to the International Pediatric Association. It was moved, seconded and carried that the sum of $125 be given to the International Committee to cover postage.

National Conference on Prevention and Control of Juvenile Delinquency:

A report from the National Conference on Prevention and Control of Juvenile Delinquency was placed on file.

American Association of Blood Banks:

A letter from the American Association of Blood Banks was tabled for further consideration.

* * *

It was moved, seconded and carried that the Secretary be authorized to sign contracts for exhibitor booth installation.

* * *

Dr. Grulee, upon his request, was released from his promise to give his library to the Academy, since there was an opportunity to place this as a separate unit in the John Crerar Library in Chicago.

The Child Safety Campaign:

The following letter, prepared for general distribution by Dr. Albert D. Kaiser, who is the Academy representative for the Child Safety Campaign, was read:

Dear Doctor:

This fall, the American Academy of Pediatrics, in cooperation with the National Safety Council, the U. S. Children's Bureau, and the Metropolitan Life Insurance Company, will attempt to focus more attention on the problem of reducing accidents in the pre-school age. Because of the remarkable improvement in communicable disease mortality, accidents now constitute the leading cause of death from 1 to 15 years of age. The chart in the attached descriptive folder shows that the greatest point of emphasis should be in the pre-school ages, where accident mortality has been reduced only 13% in the past 16 years with gains of 70 to 90% in the major childhood diseases.

As a pediatrician and a member of one of the cooperating agencies, you will be interested in the following objectives of the program:

1. To encourage public health, medical and other interested agencies, to give added emphasis to child safety in their own programs.

2. To bring information on child safety to parents, teachers, physicians, and others in the community who are concerned with the welfare of children.

3. To publicize the need for concerted effort on child safety through community groups, newspapers, and local radio stations, a speech, news release, radio script, and magazine advertisements on child safety.

A special packet of material on child safety (including recent statistical studies and a new illustrated booklet for the public) is being mailed to you under separate cover. You may wish to have copies of the booklet for distribution to your patients. A small supply can be secured by writing to the Health and Welfare Division of the Metropolitan Life Insurance Company, 1 Madison Avenue, New York 10, N.Y.

Sincerely yours,

ALBERT D. KAISER, M.D.
Representative of the Academy for
Child Safety Campaign

It was moved, seconded and carried that the Executive Board voice approval of this program.

Report of the Building Committee:

Dr. McElhenny reported for the Building Committee. It was moved, seconded and carried that the Committee be authorized to canvass individual members for donations but not industrial firms.

Badges:

The Secretary was empowered to use plastic badges for the meetings.

By-laws:

In a letter from Dr. George Pratt Hunt the suggestion was made that the By-laws be revised so that emeritus fellows would receive the journal, PEDIATRICS, without cost. It was moved, seconded and carried that no change of the By-laws be made.

Reinstatement:

It was moved, seconded and carried that the name of anyone applying for reinstatement should be circularized through the district in which he resides in the same manner as is the name of any new applicant.

* * *

A letter to go out to the members explaining the reason for the increase in dues was approved.

REPORT OF THE PUBLICATION COMMITTEE (CONDENSED)

The Committee has met on three occasions throughout this first year and much time and effort has been expended in getting orientated in our new job and establishing the proper relations between the different agencies concerned in the promotion of our new enterprise. A Publication Committee luncheon was held at the Annual Meeting in Dallas to discuss with those interested our set up and to ask for suggestions on both the editorial and business aspects of PEDIATRICS.

This Committee has been entrusted with the financial and business management of the journal to relieve the Editorial Board of all such duties so that they might have their full time to devote to the editorial work which is particularly heavy in the formative period of a new periodical of this nature. The Committee is interested in producing a first class journal which will be informative to the members and will be instructive from a scientific standpoint.

The Pease History of the Academy has been microfilmed and will await further instructions from the Executive Board as to its final disposition.

The fiscal year of PEDIATRICS has been changed to coincide with that of the Academy and thus with only six issues of PEDIATRICS we close our first year. Since the Editorial Board and this Committee were appointed over a year ago, we have a full year's expenses in some departments with only six months revenue from the journal. This has made some difference in our budget estimates for this period and a actual deficit exists.

For various reasons, PEDIATRICS has been off schedule but will, with the July issue, move into a regular program and barring labor troubles will continue to appear on time each month according to original plans.

The campaign for subscriptions has resulted in a total of 3,357 subscribers of which over a thousand are non-Academy members. Extra copies have been printed to provide for future orders for single issues or sample volumes.

To date, we have had advertisements from 49 different firms and there are many more excellent prospects to be contacted. The original estimate for this period has been greatly exceeded and should point to a healthy financial status in the future. Advertising policy has been broadened to permit any ethical firm to buy space in PEDIATRICS so long as no violation of Academy principles nor our contract with Charles C Thomas, Publisher ensues, and provided the advertising matter is acceptable to the Editorial Board.

Reprints through April total 36,450, and with the May and June issues yet to enter the picture, we will have a high average in this respect.

The budgets of both the Editor and the Publisher have been exceeded but it can be readily understood that in the process of initiation, organization, and promotion of a new venture, such as this, unpredictable expenses arise due to lack of precedent for us to follow. The budgets for the succeeding year will be submitted for your consideration.

We have been compelled to employ extra help in the editor's office due to the volume of detail work and we commend Dr. McCulloch for his interest and untiring effort in handling his own work as well as much extraneous work of noneditorial nature which has come into this office.

The Publisher's budget, originally based on 18 months time and twelve issues of PEDIATRICS has required revision and we feel that Mr. Thomas has been governed by consideration for the best interests of the Academy as well as the protection of his company and that he has made a sincere effort to aid in the establishment of our journal. There is no reason to feel that we will not profit by this connection.

For the reasons stated, publication costs have exceeded the original estimate and since the Academy is committed to underwrite any deficit, we do not take our position lightly and it will be our obligation to protect the Academy's interest, to make PEDIATRICS a financial success, and to aid in the raising of it to a high level among medical publications. The duties of the Committee will require us to meet at least once a year.

We regret to announce the resignation from the Committee of Dr. Charles F. McKhann who has been particularly valuable to us and whose counsel and advice have been very timely and constructive in the uncertain period of our beginning.

Respectfully submitted,

FRANK H. LANCASTER, *Chairman*

This report was accepted and a resolution of thanks to the Committee was voted.

The budget of the Publication Committee was submitted to the Budget Committee and after careful consideration was accepted and approved by the Executive Board.

It was moved, seconded and carried that the Executive Board authorize one annual meeting of the Publication Committee, the expense of which is to be met with journal funds.

The resignation of Dr. Charles F. McKhann from the Publication Committee was accepted.

Report of the Editorial Board:

Dr. Hugh McCulloch reported for the Editorial Board. The Executive Board confirmed the appointments of Dr. Moncrieff and Dr. Ellis as Corresponding Editors of PEDIATRICS, and of Dr. Paul Harper as an Associate to Dr. Park.

It was moved, seconded and carried that the Board express its very sincere appreciation and thanks to Dr. McCulloch for his excellent work on the journal.

The Meeting adjourned at 4:50 P.M.

Round Table Discussion

VIRAL DISEASES

RUSSELL J. BLATTNER, M.D., *Chairman, Houston, Tex.*

INTRODUCTION

Chairman Blattner: During recent years, there has been increasing interest shown in diseases caused by filterable viruses, and significant work has been accomplished in this comparatively new and absorbing field of endeavor. With the advent of chemotherapeutic agents and antibiotics, the presence and action of these infectious agents has become more apparent. Viral diseases, therefore, have assumed increasing importance in medical literature in general and in pediatric literature in particular.

By way of review, it is well to bear in mind that viruses are filter-passing agents, obligate intracellular parasites, capable of reproducing themselves and of producing disease in plants and animals, including man. While these agents cannot be seen except by the most elaborate methods, their presence can be detected by their injurious effects.

The pathologic picture produced by viral agents is rather characteristic and can be recognized readily by experienced observers acquainted with tissue response. In some instances, inclusion bodies are produced which may be intranuclear or intracytoplasmic, and represent cytologic changes which are considered typical of the pathologic response to viral invasion. When inclusion bodies are present they may serve as sign posts for the recognition of the type of infectious agent.

The nature of a filterable virus is as yet unknown. Viruses may be a form of life similar to bacteria, but infinitely smaller in size. It is conceivable that viruses are enzymes capable of reproducing themselves and capable of producing cellular response. They may be non-living, crystallizable substances, such as the Stanley tobacco-mosaic virus; or a form of life, the definite nature of which is as yet unrecognized. Dr. Thomas M. Rivers has stated: "Viruses are a heterogeneous collection of diverse agents which happen to induce a state of broad similarity." He points out that the reaction of the tissues in general, and of the cells in particular, determines the nature of the pathologic process about as much as the infectious agent itself.

The clinical manifestations of viral agents are many. Frequently it is difficult on clinical grounds alone to make the diagnosis of viral disease with any degree of accuracy. While viral disease may be suspected on clinical grounds, it usually remains for the laboratory by appropriate tests to help us make an exact etiologic diagnosis. Many advances in this field, applications of laboratory procedures in the study of viral diseases, have been made in recent years. Dr. S. Edward Sulkin, Professor of Bacteriology and Immunology at the Southwestern Medical College here in Dallas, will tell us of some of these interesting and important contributions in the laboratory diagnosis of virus disease.

Dr. Sulkin: Although it seems unlikely that the diagnosis of viral diseases will ever become as simple as diagnosis of bacterial infections, a number of procedures have been developed in recent years which facilitate identification of viral agents. The literature on this subject is accumulating with such rapidity that it is impossible to outline all the recent developments in a limited discussion. Today, therefore, we shall deal only with certain of the newer procedures which are of value in the diagnosis of this group of diseases.

Generally speaking, methods followed in the laboratory diagnosis of diseases caused by viruses are analogous to those used in bacterial infections. Conclusive evidence consists in the demonstration and identification of the virus. This may be accomplished in the case of some viral diseases by employing susceptible laboratory animals or chick embryos instead of the ordinary culture media used for the isolation of bacteria. Unfortunately, many factors may complicate direct isolation of the causative agent from the patient. The necessity for individual isolation of infected animals to prevent contact infection has been emphasized by many workers. For example, it has been shown by

From the Annual Meeting of the American Academy of Pediatrics, Dallas, December 8-11, 1947.

the British investigators that ferrets exposed to animals in the acute phase of influenza may contract the disease. This is true of many viral infections which involve the mucous membranes of the respiratory tract. Latent viruses of ordinary laboratory animals may appear during animal passage and be mistaken for that causing the disease under investigation. A number of such agents have been isolated. The possible existence of the carrier state in man must also be taken into consideration. Over 10 years ago one investigator, Gerlach, demonstrated virus in the sputum of four patients who lacked clinical symptoms of psittacosis, suggesting the human virus carrier state. More recently, Dr. Karl F. Meyer reported a case of a convalescent carrier who had harbored the psittacosis virus for a period of eight years. The presence of herpes simplex virus in tissues of persons without clinical evidence of disease is well known; this virus has been found in the cerebrospinal fluid and saliva of apparently healthy persons and in the normal conjunctival sac, and has been encountered frequently as a contaminant in viral studies.

Viral agents may persist in the tissues of various animal hosts for long periods of time. Under certain conditions the virus of St. Louis encephalitis may invade the central nervous system of susceptible mice and remain dormant there almost indefinitely. The herpes simplex virus has been detected in the brains of rabbits several months after experimentally induced infections, and the encephalomyelitis virus of mice may persist in the brain and spinal cord over a year after recovery from the clinical disease. The poliomyelitis virus has been recovered from the central nervous system of monkeys two weeks after the disappearance of paralysis and the persistent excretion of this virus in the stools of convalescents has received considerable attention.

Primary isolation of a viral agent in experimental animals often fails because of the small concentration of virus in the original specimens. This objection has been overcome to some extent by the use of the so-called blind passage technic which permits greater multiplication of the virus in the passage animal. Although the virus of Japanese B encephalitis may be isolated from the blood and spinal fluid and is sometimes detectable in the urine, it is often necessary to resort to this procedure for successful isolation of the agent. Recently, Koprowski and his colleagues employed this method in the isolation of poliomyelitis virus from human serum by direct inoculation into mice. This, incidentally, represents the second reported instance of demonstration of this virus in human blood and it is the first report of successful isolation of the agent from the blood of humans by direct inoculation of laboratory mice. Other viral agents, however, have been isolated from the blood in a number of instances. It has been shown that viremia in lymphocytic choriomeningitis may persist as long as two weeks. Some time ago, Howitt recovered the virus of Western equine encephalomyelitis from the stored blood serum of an adult whose illness had been diagnosed as encephalomyelitis. And recently, Blattner and Heys isolated the St. Louis encephalitis virus from the blood of a patient whose clinical manifestations were suggestive of a virus infection with minimal central nervous system involvement. Incidentally, this was the first instance of isolation of this virus from a human subject during life. In 1946, Beeson and his associates reported isolation of the virus of lymphogranuloma venereum from the blood and spinal fluid of one of eight proved cases of the disease. While it is true that in most cases suspected of viral etiology, the blood of the patients represents an excellent potential source of the virus, a number of factors should be considered when isolation of a virus from the blood is being attempted. The specimen should be drawn as soon as possible after the onset of illness, since the rise in antibody during later stages of the disease may cause the disappearance of the virus from the bloodstream.

A number of acceptable methods are available for the primary isolation of viruses. Complications resulting from the use of the experimental animal have already been discussed. Although a number of viral agents have been propagated in tissue culture, the method has had only limited use as a diagnostic tool thus far; the virus of epidemic keratoconjunctivitis having been isolated by Sanders by this means. The fertile egg, on the other hand, is now widely used and has been found to be applicable to the study of a variety of viral problems. The many factors which complicate the use of experimental animals may be eliminated by the use of the chick embryo. Isolation to prevent contact infection or cross infection is not necessary when fertile hen's eggs are used. In addition, latent viruses of ordinary laboratory animals which frequently confuse diagnosis are unknown in the developing chick embryo; no report has appeared in the literature of the occurrence of a viral agent in uninoculated eggs. The possible existence of unsuspected natural or acquired immunity which may complicate the use of laboratory animals does not interfere with the use of chick embryos since the latter are not able to produce antibodies.

The necessity for using bacteriologically sterile material for chick embryo inoculation is, to be sure, a limitation to its use in virus study. But this has been largely overcome by the use of ether, zephiran and the antibiotics and sulfonamide compounds to rid specimens of bacterial contaminants. The use of bactericidal agents obviates the need for filtration which is frequently unsatisfactory because the viral agent may itself be retained along with the undesirable bacteria. A number of reports have appeared in the literature concerning the usefulness of these bactericidal agents. Ether may be used to destroy bacterial contaminants without affecting the poliomyelitis, rabies, and measles viruses. It has long been used in preparing fecal specimens for demonstration of poliomyelitis virus. Zephiran has been found satisfactory for the isolation of the influenza virus from throat washings, although it is not consistently effective. It has been shown that the growth of influenza virus is favored, and the life of the chick embryo tends to be prolonged, when penicillin is used. The isolation of the epidemic parotitis virus directly from human saliva by inoculation into the amniotic cavity with penicillin has been reported by Australian investigators. Only a few months ago, Duffy and his colleagues established a diagnosis of rabies in an infant by isolation of the virus from penicillin-treated saliva. Dr. Harford and I had previously isolated this virus from human saliva which had been treated with ether. Morgan recently found streptomycin and tyrothricin useful in the isolation of psittacosis virus from fecal material by direct inoculation into the yolk sac of developing chick embryos. The sulfonamides, alone and in combination with antibiotics, have proved useful in eliminating bacterial contaminants from specimens examined for various viruses. It is evident from these and similar observations that the presence of contaminating bacteria in specimens submitted for virus studies no longer constitutes a serious handicap.

Within the limits of this discussion it is impossible to review all of the procedures used in the laboratory diagnosis of viral diseases. We shall attempt, however, to review the most important tests, and consider their advantages and disadvantages. The neutralization test, which is widely used for detecting the presence of virus neutralizing antibodies, presents many disadvantages as a diagnostic procedure for the use in the general laboratory. Routine use of this test is not feasible because of the complicated and cumbersome procedure involved. The inoculated animals must be observed frequently for a long period of time before results become available. Usually, neutralizing antibodies do not appear until after convalescence is well under way so that the diagnosis is delayed. In some cases animals must be strictly isolated to prevent contact infection, as discussed previouly. We have also mentioned the possible presence of latent viruses of ordinary laboratory animals or accidental infection of experimental animals which may complicate interpretation of results. In addition, there is no unanimity of opinion as to the technical conduct of the test, though efforts are being made to standardize the procedure. An obvious drawback to the general use of this test is the highly infectious nature of the material used. This is evidenced by the large number of proved cases of viral infection contracted in the laboratory. Over a hundred cases with at least 14 fatalities have been reported in the literature. Recognized accidents accounted for only 11 of these cases. In addition to these instances of recognized illness, there have been an unknown number of inapparent infections as shown by the acquisition of antibodies by numerous laboratory workers.

Because of difficulties complicating the use of the neutralization test, attempts have been made to develop simpler procedures for use in the general laboratory. The complement fixation test presents many advantages over the more cumbersome neutralization test. The procedure is familiar to most laboratory workers and no animals are required aside from those used in the production of antigen. Furthermore, results are usually available within a few hours. The biologics used in the test, though requiring specialized technic for their preparation, are becoming available for general use. At the present time the preparation of antigens and positive antisera for control tests is too specialized a procedure for the ordinary serologic laboratory. It has been suggested that this may be obviated if necessary materials for diagnostic studies are supplied to regional laboratories. This is now possible for work with the virus of lymphocytic choriomeningitis, since both the noninfectious specific soluble antigen of this virus and its corresponding antibody are relatively stable under ordinary conditions, and this antigen can be dried from the frozen state, stored, and shipped without deterioration.

A number of improvements which have been introduced in recent years have increased the practicability of the complement fixation test in the viral field. A test for lymphocytic choriomeningitis with a soluble antigen extracted from the spleen of infected guinea pigs was developed in 1939 by Smadel and Wall. Procedures designed to eliminate anticomplementary effects of brain tissue

antigens and sera, and non-specific reactions between antigens and antisera have been described by workers at the Rockefeller Institute and others. Undesirable tissue components have been eliminated from infected nervous tissue antigens by alternate freezing and thawing followed by centrifugation. The non-specific effects so frequently encountered in complement fixation tests with viral antigens have been eliminated from antisera by submitting them to the action of heat. Because of the increased interest in the development of complement-fixing antigens derived from chick embryos and mouse brain tissues, DeBoer and Cox recently undertook development of antigens free from non-specific factors and found that such antigens for a variety of neurotropic viruses could be prepared without appreciable loss in antigenicity by extraction in the dessicated state with benzene.

Because of the obvious limitations to the use of diagnostic tests in which infectious material which may induce disease through accident or carelessness must be used, several investigators have undertaken the preparation of non-infectious antigens. Attempts have been made to render viral preparations inactive by the use of chemical or physical means without destroying their antigenic properties. The inactivation effect of ultraviolet light on viruses has been observed by several workers, and some investigators have described successful freezing and drying of small amounts of ultraviolet irradiated non-virulent antigens permitting their use in the complement fixation test over long periods of time.

A great deal of progress has been made in the development of a specific and practical complement fixation test for diagnosing central nervous system viral infections. It has been shown that this test is a valuable laboratory aid both in the diagnosis of sporadic cases of encephalitis and in establishing the etiology of an epidemic. The test was applied in a severe outbreak of Western equine encephalomyelitis in man which occurred in the North-Central states and in some Canadian provinces during the late summer and early fall of 1941. This outbreak occurred simultaneously with an epidemic of poliomyelitis making the clinical diagnosis very confusing. With the aid of this procedure, Hodes and his associates showed that an outbreak of encephalitis which occurred on Okinawa during the summer of 1945 was due to Japanese B encephalitis virus. The practicability of the complement fixation test has been confirmed in our laboratory and the procedure appears eminently useful as a diagnostic aid. In addition to its use with the viral encephalitides, this test has been found to be of practical value in the diagnosis of a number of other diseases of viral etiology, including influenza, lymphogranuloma venereum, yellow fever and epidemic parotitis. According to Kane and his associates, the complement fixation test is of particular value in the diagnosis of those cases of acute aseptic meningoencephalitis in which previous involvement of the salivary glands was inapparent.

The discovery in 1941 by Hirst, and independently by McClelland and Hare, that influenza virus possesses the capacity to agglutinate erythrocytes, provided a valuable new approach to the study of viral agents. The so-called hemagglutination test is now widely used in the diagnosis of epidemic influenza, and the antigenic pattern of strains of influenza isolated during different epidemics has been compared by this technic. It is now known that other agents, including those of vaccinia, variola, fowlpox, Newcastle disease, ectromelia of mice, epidemic parotitis, etc., cause specific agglutination of erythrocytes. In addition, it has been shown that the Hirst agglutination phenomenon is exhibited by certain rickettsiae. With all of these agents the agglutination of erythrocytes may be inhibited by the addition of specific immune serum; for this reason the reaction has already been widely applied to various aspects of viral research. It has been suggested that the hemagglutinative property becomes manifest only after adaptation of certain viruses to the developing chick embryo. This may account for the previous failures to demonstrate hemagglutination when monkey gland epidemic parotitis virus was mixed with suspension of red blood cells. Recently, however, Beveridge and Lind of Australia, isolated two strains of parotitis virus from human penicillin-treated saliva by inoculation into the amniotic cavity of the chick embryo, and hemagglutinin was detected after three to four days' incubation. It has been suggested that the hemagglutination test with this virus may provide a more rapid and convenient diagnostic method for detecting increases in antibody concentration than other serologic procedures. The difficulties which have been encountered in attempts to standardize the hemagglutination procedure will not be discussed at this time. The mechanism of the phenomenon is being explored by a number of workers, and attempts to eliminate false positive reactions are being made.

In conclusion, I should like to comment on recently developed skin sensitivity tests. A cutaneous

sensitivity test is of particular value under circumstances where facilities for examining serum for specific antibodies are not readily available, or if difficulty is encountered in obtaining a specimen of blood as, for example, in pediatric practice. Skin tests have been described for vaccinia and lymphogranuloma venereum several years ago. The Frei intradermal test for lymphogranuloma venereum is the only viral disease in which a skin test is now widely used as a diagnostic aid. With improved methods for growing viruses in high titer, there is reason to believe that intradermal reactions will be employed with increasing frequency. In recent years a number of other intradermal tests with antigens of viral origin have been introduced. About a year ago Nagler reported specific dermal reactions in herpetic persons receiving intracutaneous injection of heat-inactivated herpes virus cultivated in the chick embryo. Since a positive reaction could be correlated with the presence of circulating antibody, this test may eventually be of value in differential diagnosis. Blattner and his associates, and other workers, have shown that primary herpetic infections may appear as a complication of infantile eczema. Zarafonetis, Whitman and others have shown that the herpes simplex virus may invade the central nervous system producing an acute encephalitis which is indistinguishable, clinically, from other virus encephalitides. Quite recently, Rose suggested that since primary herpetic infections occur chiefly in early life the dermal sensitivity test with the virus of herpes simplex may find its widest field of application in pediatric practice. The Australian investigators demonstrated that influenza virus produces a cutaneous reaction in most adults and in some children and suggested that allergy to the virus may play a part in resistance to infection. Whether or not this reaction will be useful in determining susceptibility to influenza remains to be seen.

A dermal sensitivity test for epidemic parotitis using heat-inactivated parotid gland of virus infected monkeys or irradiated allantoic fluid virus as antigen may be of value in diagnosis of this disease. According to Enders and his colleagues, about 90% of the persons exhibiting erythematous dermal reactions of greater than approximately 14 mm. in diameter 48 hours after inoculation of this material may be, from the practical standpoint, considered resistant to parotitis. Dermal sensitivity tests will undoubtedly be further investigated because of their potential importance as diagnostic procedures.

On the basis of the foregoing information it can be seen that while the diagnosis of viral diseases is at this time beset with difficulties, and is a relatively specialized technic, progress is being made toward developing simplified diagnostic procedures. These tests offer to the clinician an objective means of confirming a diagnosis which cannot be made on a purely clinical basis. Unfortunately, to date, methods available permit diagnosis only after the patient is convalescent or has died; however, practicing physicians are urged to make use of the facilities for diagnosis of viral infections, wherever they are available. Physicians should learn what materials should be collected for the various tests and arrange for them to be delivered to the laboratory in condition suitable for examination.

Chairman Blattner: From a clinical standpoint we often encounter difficulty in making an etiologic diagnosis with certainty. Dr. Florence Heys, Instructor in Pediatrics at the Baylor University College of Medicine, Houston, Texas, will tell us of her experiences in the isolation of virus in the diagnosis of certain skin diseases in human subjects.

Dr. Heys: The exact diagnosis of the various exanthemata characterized by vesicular-pustular lesions is often difficult. In some of the cases a satisfactory etiologic diagnosis can be made only by the isolation from the lesions of an infectious agent which can be subjected to careful laboratory studies. As Dr. Sulkin has pointed out, the various agglutination tests, complement-fixation and skin tests are being improved, are proving more sensitive than was supposed possible, and are of value in diagnosis especially in following antibody titers. However, the isolation and identification of the infectious agents, as well as the demonstration of increasing titer of type-specific antibody, are to date the most satisfactory means of diagnosis. Such identification of the infectious agent is of academic interest and may be of practical importance.

The fertile egg technic has yielded good results especially since the availability of antibiotics has facilitated the separation of virus from many of the common bacterial invaders. Presumptive evidence as to etiology is provided by the demonstration of increasing titer of type-specific antibody in the patient's blood during the course of clinical recovery.

I should like to present findings in a series of cases from the skin lesions of which virus was isolated and identified by laboratory studies.

Herpetic Infections:

1. Two Cases of Kaposi's Varicelliform Eruption. Kaposi's varicelliform eruption is a comparatively rare exanthem occurring in patients with atopic eczema or some form of neurodermatitis. The illness is characterized by high fever, by leucopenia and by the presence of umbilicated vesicles which usually become pustular. The disease is self-limited and in general the prognosis is good. However, this disease does constitute a grave systemic infection and fatalities do occur when acute encephalitis develops or in cases where superimposed bacterial infection of the skin is extensive. Bronchitis and bronchopneumonia are not uncommon complications.

The condition was first described in 1887 by Kaposi who considered it an alarming complication of infantile eczema. Kaposi classified the eruption as varicelliform, at the same time pointing out that herpetiform might apply as suitably. While nothing definite as to etiology was stated, it was suggested that the "epidermis loosened by eczema" might be "suitable soil" for the growth of a fungus or some other infectious agent.

In the years that followed these statements there was considerable discussion as to etiology. Regardless of the fact that in most instances bacteria were isolated from the lesions, the general concensus favored viral etiology, and various attempts at isolation were made. Many associated the eruption with the virus of vaccinia in spite of the fact that the exanthem occurred in patients who had been vaccinated months or years previously and that patients who recovered could be vaccinated successfully.

In 1943 and 1944 Barton and Brunstung reported isolation by corneal inoculation of rabbits of a strain of herpes virus from the cutaneous lesions of a patient diagnosed as Kaposi's varicelliform eruption. Reviewing the literature, they found only 67 cases to that date. Fifty-three of the patient had a history of chronic allergic dermatitis. Others had been subject to seborrheic dermatitis, sycosis vulgaris, simple trauma, impetigo or scabies. Fifty-one were in children.

About the same time Wenner, working independently, isolated herpes virus from the cutaneous lesions of four patients, and in one of these from brain tissue taken at autopsy.

During this period likewise investigations were under way on our first case, a child of 15 months with a history of atopic eczema. In this case the disease was mild. Fluid from cutaneous lesions on the fifth and sixth days of illness was cultured for bacteria, pure cultures of Str. hemolyticus and Staph. aureus resulting. At the same time material from the cutaneous vesicles was inoculated on the scarified cornea of a rabbit and onto the retracted chorio-allantoic membrane of the developing hen's egg. By these means, two strains of herpes virus were isolated which were established readily by corneal passage, egg passage and by transfer to mice and hamsters by intracerebral inoculation. The agent proved filterable—V13 and N-filters. Encephalitis in rabbits was apparent within nine to eleven days following inoculation by corneal scarification. The virus was found to be infective for mice at 10^{-8} in eight to nine days. Inclusion bodies were demonstrated readily in the mouse brain, the chorio-allantois and the cornea of the rabbit and were identified as the herpetic type.

The patient developed during clinical course increasing titer of type-specific humoral antibody to the virus isolated from his lesions and to a known strain of herpes (HF). Serum-viral neutralization tests in white mice were used in following antibody titer. Tests for specific antibody to the virus of vaccinia were carried out by means of egg protection tests and none was detected.

More recently we have carried out similar studies on a young adult patient, a 21-year-old male, with Kaposi's varicelliform eruption. This patient had a history of atopic eczema and neurodermatitis. The patient was very ill with extremely high fever and prostration. Again Str. hemolyticus and Staph. aureus were isolated from the cutaneous lesions. As before, the virus was isolated by two methods: corneal inoculation in the rabbit and by inoculation of the chorio-allantois. The use of the chorio-allantoic membrane precludes any possibility that latent virus in the rabbit was activated by scarification. In this instance instead of Seitz filtration of the material, penicillin was added, 1000u/cc in broth. This controlled bacterial invaders adequately. Virus was isolated readily, established in mice, eggs and by cornea. The infectious agent was shown to be filterable, and infectious for mice as far as 10^{-7} one-half the mice dying in 10 days. Convulsions and death resulted in rabbits within 12 to 15 days following inoculation by scarification. The virus was identified as a member the herpes group. The patient developed during clinical course type-specific antibody to the virus from his own lesions and to a known (HF) strain of herpes.

Also in 1947, two cases of Kaposi's varicelliform eruption have been described in adults by Barker and Hallinger. Herpes simplex was isolated by corneal inoculation of the rabbit. These

authors distinguish two forms of the disease as illustrated by their two cases: one a severe form occurring in a person with preexisting chronic dermatitis and the other, a milder form occurring in a patient with no skin irritation but who had apparently met the virus for the first time by contact with a person with severe labial herpes and stomatitis. These authors conclude that the disease is a systemic infection as well as a widespread cutaneous manifestation.

2. Another skin manifestation which we have encountered in children is that which results from autoinoculation.. Two cases of meningitis, one meningococcus and one pneumococcus in children aged two and two and one half years respectively, and one case of lobar pneumonia in a three-year-old child, developed labial herpes during their clinical courses. In all three of these children auto-intoxication of the herpes virus on fingers or arms resulted from scratching or sucking. Herpes simplex was isolated from the lesions, and increasing titers of type-specific antibody were demonstrated. It is of interest that in the most severe of these the antibody titer showed very slow rise during the period when the lesions were healing. Complete protection was not shown by the tests until some time after the lesions were healed.

Variola:

From the second group of cases, four in number, the virus of variola was isolated. The first case was that of a 69-year-old grandmother who had contracted the disease from her granddaughter. On the fourth day of the exanthem fluid from cutaneous vesicles was inoculated onto the retracted chorio-allantois. Within three days good growth characteristic of variola was observed on the membrane. During clinical course the patient developed increasing titer of antibody to a known strain of vaccinia and to the virus which had been isolated from her skin lesions. Antibody titer was followed by means of the egg protection test.

The second patient was that of a 17-year-old boy, in whose case the same procedures were followed. Two other cases have been identified by these means, a ten-year-old Negro girl and a nine-year-old Negro boy. The egg technic is useful also in differentiating variola from severe varicella; the latter virus apparently does not grow on the chorio-allantois. We have seen several cases of severe varicella which simulated variola. In these the clinical differential points were not as definite as usual.

Generalized Vaccinia:

In a third group of cases which I will summarize briefly, vaccinia virus was the infectious agent isolated.

1. Child, girl of two years; no history of atopic eczema; mother noted skin irritation on the seventh day following vaccination; eighth to ninth days, fever rose to 40°C.; lesions became pustular; diagnosed impetigo. Child admitted to the hospital on the 17th day following vaccination because of failure of impetigo to heal. On admission vesicular-pustular rash severe, new vesicles forming, umbilicated lesions. Obvious superimposed pyodermia. Two strains of Staph., aureaus and albus and a Str. hemolyticus were cultured from vesicular fluid. After Seitz filtration the virus of vaccinia was isolated by means of the chorio-allantois. Egg protection tests showed the titer of type-specific antibody very slow in rising, i.e. three weeks after admission to the hospital—about five weeks after vaccination, before the level of antibody was reached which is reached usually by the third week following uncomplicated vaccination.

2. The second child of this group was a boy of five months with a history of atopic eczema since one month of age. He was thought to have been exposed to a vaccinated sibling. As in the case of Kaposi's varicelliform eruption only the eczematous portions of the skin were involved. The virus of vaccinia was isolated from the skin lesions by the fertile egg technic—and the patient developed increasing titer of antibody to known strain of vaccinia. Antibody titer was followed by egg protection test.

Localized Vaccinia:

A fourth group of cases we have classified as localized vaccinia. These may be summarized as follows:

1. Twenty-month-old girl; vaccinia of right eyelid; lesions on the margins of the lids. Contact apparently by washcloth of vaccinated sibling. No corneal involvement. Complete recovery with small scars on lids. Virus of vaccinia isolated by the fertile egg technic. Child developed increasing titer of antibody.

2. Negro child, 16 months. Vaccinated three weeks before admission. One week following vaccination child was severely burned on arm. Seven days after the burn, rash appeared on body, followed by isolated vesicular lesions; area of burn showed mass of vesicular-pustular lesions. Staph. albus was cultured from the burn area and other lesions; the virus of vaccinia was isolated from the burn area and other lesions.

Dr. Sulkin: About two years ago a dermatologist submitted material from two cases which he diagnosed as Kaposi's varicelliform eruption. From one of these patients, a young adult, we isolated a filterable virus which was identified as a member of the herpes group. The agent was recovered by inoculation on the scarified cornea of the rabbit and by inoculation on the chorio-allantoic membrane of the developing chick embryo, as described by Dr. Heys. I, too, would recommend that both procedures be employed. The chick embryo technic is especially useful because latent viruses of ordinary laboratory animals which frequently confuse diagnosis are not known to occur in the developing hen's egg. As pointed out earlier by Dr. Blattner and by Dr. Heys, this dual technic also would exclude any possibility of a latent herpes virus being reactivated in the rabbit which is being inoculated.

Chairman Blattner: It is of interest to point out that for so many years the etiology of Kaposi's varicelliform eruption was uncertain, and then within the course of about six months, investigators working independently in three laboratories isolated the virus of herpes from skin lesions, in New Haven, in Saint Louis, and in Rochester, Minn.

This illustrates very well the fact that when a laboratory procedure becomes available, it does not take long for various laboratories to make use of it. The cooperation which the laboratory worker has from the clinician is very important. The laboratory worker as a rule has no way of knowing what patients are in the hospital unless the clinician requests study. Nine times out of ten, the clinician will refer things which are not really of great interest. However, the laboratory worker is willing to take our errors nine times for the tenth time when some referral results in the isolation of a specific agent. Dr. Sulkin and Dr. Heys could not have accumulated all of this interesting material if they had not had the cooperation of the clinicians.

Dr. John Adams, the next speaker, is Associate Professor of Pediatrics at the University of Minnesota. He has been very much interested in the respiratory viruses.

Dr. Adams: The great majority of respiratory diseases are still unknown etiologically—consequently such diagnoses as we frequently make of bronchitis, nasal pharyngitis and the too-often-made diagnosis of "flu" are getting to be rather meaningless terms. Unfortunately we do not have readily available practical laboratory tests for isolating etiologic agents in respiratory diseases, so we have to rely on clinical, pathologic, and epidemiologic evidence.

The Commission on Acute Respiratory Diseases has experimentally transmitted minor respiratory illnesses to human volunteers and has demonstrated that at least two filtrable agents, presumably viruses, can induce minor illnesses in man. These illnesses are distinct disease pictures, the first has a short incubation period of one to two days, is characterized by sneezing, nasal obstruction, coryza and cough. The second has a five to six day incubation period and is characterized by sore throat and few nasal symptoms. In a second experiment they tested homologous and heterologous immunity to the two agents producing the diseases. Immunity to reinoculation was found in individuals who previously developed the sore throat type of illness with the five to six day incubation period; little or none was found in subjects challenged with the filtrate which produced the coryza-like illness of one to two days incubation period. Cross-immunity was not demonstrable with either filtrate. Primary atypical pneumonia developed in three volunteers following inoculation of filtrate from a single donor who had atypical pneumonia, and each of these three patients had had one or more previous inoculations with the two filtrates responsible for the previously mentioned mild respiratory illnesses. These results provide additional proof that at least two filterable agents, or viruses, may induce minor respiratory illness and suggest that these agents may be distinct from the virus or viruses which produce primary atypical pneumonia.

Exudative Tonsillitis and Pharyngitis

This disease is rare in the period of infancy but following this period it is one of the commonest diseases of childhood and therefore deserves some detailed considerations. The assumption that Str. hemolyticus, beta is the cause of this disease entity is in the majority of instances incorrect. The Acute Respiratory Disease Commission demonstrated that in carefully controlled and studied cases

that over half of all cases had neither bacteriologic nor seriologic evidence of streptococcal infection.

Because less than half of the cases of exudative tonsillitis and pharyngitis are due to the Str. hemolyticus, beta it is necessary to consider the symptoms and signs of these two disease pictures comparatively. The results of the Commission's studies are based on an anlysis of 54 cases in which both bacteriologic and serologic observations indicated that the Str. hemolyticus, beta was the causative agent and from another group of 125 cases in which the above procedures failed to show evidence of infection by this organism.

The streptococcal infections have a more acute onset. Chilliness, feverishness, headache and malaise are more common in this group but the difference is slight. The incidence of horseness, sputum and chest pain are more frequent in the non-streptococcal patients. The differential diagnosis is aided by the physical examination which reveals diffuse redness of the mucous membranes of the palate, tonsils and posterior pharyngeal wall with edema in the streptococcal cases. The presence of enlarged and tender lymph nodes is a striking differential point being the usual finding in the latter group.

The average leukocyte count in streptococcal tonsillitis and pharyngitis was 13.4 thousand and 79% polynuclear leukocytes, and 9 thousand with 67% in the non-streptococcal cases.

The fever and general severity of illness is slightly greater in the streptococcal group. The exudate in these cases is usually yellow and large in extent, frequently confluent. In contrast the other patients have a white or gray, pinhead size exudate. It should be emphasized that the exudate may not manifest itself for 12 to 24 hours after the onset of symptoms. The differential diagnosis still remains difficult as this picture has considerable variability between the two groups and accurate diagnosis rests on the employment of both cultural and serologic methods. The results of bacteriologic tests are not sufficient alone for diagnosis as many patients are carriers of Str. hemolyticus beta, but in these cases usually only a few organisms will be found. Non-streptococcal tonsillitis and pharyngitis is a benign disease without complications; whereas, serious sequelae may follow streptococcal throat infections. This fact puts a high premium on accurate diagnosis. Large numbers of streptococci are usually found in the strpetococcal infections. This point would be important in deciding upon therapy as serologic differential tests are of no avail until late in the disease. In home practice it is wise to treat the seriously ill cases specifically. If a careful search for complications reveals none and if there are no tender or enlarged cervical nodes, it would be safe to assume that the patient will have a self-limited illness of three to four days and require no specific therapy.

Attention is called by the recent report of the Acute Respiratory Disease Commission to the epidemiologic relationship between undifferentiated acute respiratory disease and non-streptococcal exudative tonsillitis and pharyngitis. Likewise, the similarity in the clinical pattern is definite and non-streptococcal tonsillitis and pharyngitis may be considered a variant of epidemic undifferentiated acute respiratory disease.

The complications are confined almost entirely to the proven streptococcal cases as the others have a benign uncomplicated course. Cervical adenitis is a part of the disease and probably should not be considered as a complication. On the other hand, its very presence may indicate the streptococcal type of infection and should therefore indicate specific treatment. Penicillin is the drug of choice, although sulfonamides are also effective.

Epidemic Influenza A and B

Influenza is an epidemic viral disease, highly communicable, which primarily affects the respiratory passages. Epidemics of influenza type A are now established as occurring at fairly regular intervals of two or three years, usually beginning in the late fall or winter months. The last few epidemics of influenza type B have occurred at approximately four-year intervals. It is important to recognize this fact as the diagnosis of influenza should not be made except during an epidemic. Its sporadic incidence is known to be rare.

In the study of an epidemic of influenza occurring in infants and children, the disease was characterized by irregular or biphasic fever curves. Leukopenia was not found to be present. Acute pharyngitis, often hyperemic, and lassitude were the most prominent physical findings. None of the patients manifested severe laryngitis or croup.

Influenza A virus was isolated from throat washings taken from a number of the patients and inoculated intra-allantoically into developing chick embryos. The serologic diagnosis of the epidemic was established by the demonstration of significant increases in neutralizing antibodies by means of the hemagglutinin-inhibition test. The neutralizing antibody response of infants, who in all

probability were having their first infection with influenza A virus, was found to be of approximately the same magnitude as that of older children.

Primary Pneumonitis in Infancy

The pneumonias of early infancy are a different clinical entity than those seen in older children and often cause a high mortality. Primary pneumonitis in infancy is characterized by a high contagious rate and tends to occur in epidemics. It would appear to be spread to the infant by adults with common upper respiratory disease. The prematurely born are high susceptible even though they may be several weeks or months old. Sneezing, cough, low grade fever associated with dyspnea and cyanosis are the outstanding symptoms and signs. Dyspnea with retraction of the soft parts of the chest and cyanosis may be the first symptoms. The findings are minimal with scattered fine rales being about the only pulmonary signs; the X-ray reveals low diaphragms with over aeration, some increase in markins and soft infiltrative shadows, often confined to the upper lobes. Atelectasis, especially of the right upper lobe, is commonly encountered. The laboratory studies reveal normal blood counts, and no significant bacteria have been found in the throat cultures. Pharyngeal smears show large numbers of cytoplasmic inclusion bodies in the epithelial cells. Autopsied material from epidemics studied by us shows characteristic interstitial pneumonitis, destructive and proliferative changes of the bronchiolar epithelium with mononuclear infiltration. In the lining bronchiolar epithelium many cytoplasmic inclusion bodies have been found, similar in size and staining characteristics to those found in the pharyngeal smears.

Chairman Blattner: Since specific therapy of virus infections has been so inadequate, a more complete knowledge concerning the natural history of viral disease will be of great value and may lead to prevention and possibly to epidemiologic control.

This brings us to the last portion of the program, a presentation concerning the natural history of St. Louis encephalitis. For some years we have been interested in the epidemiology of this disease entity. It was a new disease in 1933. As resident in pathology I had the opportunity of observing some of the early work. This is a disease of great historic importance since it represents the first instance in which a virus was isolated from the brain of a human subject who died with encephalitis. In July of 1933 a sudden outbreak of "brain fever" occurred and soon reached epidemic proportions. By October there had been over 1100 cases observed. The mortality rate was approximately 20%. Clinically the disease was characterized by sudden onset, high fever, headache and meningeal signs. Recovery occurred usually in seven to ten days. The patients who died were for the most part older people who had in addition to the acute disease some organic disease. During this epidemic Muckenfuss and McCordock isolated a filterable virus by inoculation of monkeys. Subsequently Webster established the virus in white mice. The agent isolated was soon recognized as a new virus, never before identified. Clinically St. Louis encephalitis, as it was called, was recognized as a condition separate and distinct from type A encephalitis. In 1937 another epidemic occurred, again starting during July and declining in October. This time more children were involved and during this epidemic the mortality rate was about 30%. Certain features of the disease were of interest from the epidemiologic standpoint; for example, the disease occurred first in Saint Louis County in wooded areas adjacent to a small stream. In the crowded areas where we are accustomed to see epidemic meningitis and rheumatic fever, there were no cases of encephalitis. There was very little evidence of case to case transmission. There was little evidence of multiple cases in a single family. In the years since 1937, we have been able to demonstrate that an endemic focus exists in the Saint Louis area since we showed by appropriate tests that several cases of Saint Louis encephalitis occurred each year. All of these cases occurred in the summer. For some years, and as recently as 1940 when Neal's book on "Acute Encephalitis" was published, the concensus favored transmission by the respiratory route. While early experiments with mosquitoes were inconclusive, it seemed to us that Saint Louis encephalitis was not a respiratory disease, but probably one transmitted by some blood-sucking vector. In experimental work begun in 1941 Dr. Heys and I demonstrated that the common dog tick is capable of acquiring the virus of Saint Louis encephalitis, of transmitting the virus to susceptible animals by bite and of transferring the virus to its offspring by congenital passage.

Since no history of tick bite was obtained in any of these cases identified as the Saint Louis type, we did not consider the tick of real epidemiologic significance. However, it did seem of importance to have demonstrated that an arachnid vector could transmit this virus to animals, producing central

nervous system infection with convulsions and death. On the basis of laboratory studies we postulated that the virus could remain in nature in the body of the tick, that the tick feeding on animals might transfer sufficient virus to animals so that mosquitoes, or some other blood-sucking vector, might acquire the virus from such animals. Mosquitoes might be responsible for carrying the virus to other animals including man.

Hammon, Reeves and their co-workers made this significant observation. They found that culicine mosquitoes collected in nature during epidemics contained the virus of St. Louis encephalitis, and that such mosquitoes could transmit the virus to chickens by bite. There were still many questions to be asked.

Where is the virus residing when there is no evidence of an epidemic? Why does the epidemic appear suddenly in certain localities? Why are we able to demonstrate a few cases in non-epidemic years? In other words, we have felt that the virus is harbored somewhere in nature. Howitt made a significant contribution, the discovery that birds, especially barnyard fowl, have specific antibodies to the virus of St. Louis encephalitis. In attempting to make some epidemiologic evaluation of all these observations we surmised that some arthropod must be transferring the virus to birds. Dr. Smith, Dr. Heys and I spent much time mulling over this subject. In the meantime Dr. Smith was pursuing some investigations which she had in progress and which had reference to the presence of antibodies to St. Louis encephalitis in human subjects. These studies showed that persons who had come to the St. Louis area since 1937 were not acquiring antibodies to the virus of St. Louis encephalitis; whereas, a significant percentage of those tested who were residents of long standing and had lived in the St. Louis area through the epidemics, showed antibody. In studies on fowl in the same areas antibody of appreciable level was demonstrated in chickens hatched the previous spring. It seemed logical to suppose that some vector was feeding on chickens which was not feeding on a large number of human beings. With the tick investigations in mind we looked for another arachnid. There are three groups of arachnids: the spiders, the mites and the ticks. The mite has a life cycle similar to that of the tick.

On this basis we collected chicken mites in St. Louis County. The first site was a house from which a child had been hospitalized. The clinical picture suggested the diagnosis of encephalitis. Chicken mites collected from the chicken house on this property were ground up and the supernatant material was injected into mice. The virus of Saint Louis encephalitis was isolated and the strain was established in mice and eggs. Collections in other localities in Saint Louis County were made. Mites from two other sites, six and 10 miles distant from the original, were shown to harbor virus. Thus a neurotropic virus was isolated from nature in a non-epidemic year. Laboratory studies verified that the life cycle of the mite is similar to that of the tick. We were able to demonstrate that the newly identified virus is transmitted to the female mite through the egg and all stages of subsequent development into the next generation. By establishing laboratory colonies we were able to carry this observation through countless generations. Once a colony of mites is infected with the virus of Saint Louis encephalitis, either naturally or experimentally, it remains infected for all time apparently. We have colonies, established in small individual chicken houses more than three years ago, which still harbor the virus of Saint Louis encephalitis. By inference, this would mean that any chicken house infested with mites carrying the Saint Louis virus, would constitute a reservoir in nature ready to be tapped if there is some link to cause a break through to the human population. Experimental studies revealed that chickens fed upon by these infected mites have virus in their blood for from one to four days following the bite of mites.

Transmission studies with mosquitoes were undertaken in this connection and at this time Dr. Albert Miller, entomologist from the School of Tropical Medicine and Public Health at Tulane, became associated with the work. If mosquitoes of the proper type are allowed to feed on chickens during the period of viremia, such mosquitoes can acquire the virus and can transmit the virus to other warmblooded animals.

Briefly then, the concept is this: the epidemiology of Saint Louis encephalitis involves two blood-sucking vectors, one an arachnid or some similar form, in which the virus can be maintained as a reservoir in nature, and the other an insect, which feeding on chickens, or some other fowl or bird, may acquire the virus and carry it to other animals and to human beings. We were able to show that the virus remains in the body of the mosquito for as long as 35 days. Such a concept solves some of the riddles of the epidemiology of this disease, and it also explains the sudden explosiveness of an epidemic.

Pediatrics

VOLUME 2 OCTOBER 1948 NUMBER 4

SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

EDWARDS A. PARK, M.D., *Editor,* PAUL HARPER, M.D., *Associate*

INTRODUCTION

FOUR pediatricians, all members of the Academy, are deans of important medical schools: Dr. Vernon W. Lippard, Dean of the University of Louisiana School of Medicine; Dr. Wilburt C. Davison, Dean of Duke University School of Medicine; Dr. John McK. Mitchell, Dean of University of Pennsylvania School of Medicine; and Dr. Francis Scott Smyth, Dean of the University of California School of Medicine. I thought it would be interesting to obtain the answers of these four important administrators to the question of the acceptance of federal funds for the advancement and extension of pediatric education.

The letters from these pediatricians are complemented by one from Dr. George S. Stevenson, who is medical director for the National Committee for Mental Hygiene, Inc., and so is in a strategic position to have observed the operation of Federal grants-in-aid to educational institutions under the National Mental Health Act. His observation that in the administration of this program the U.S. Public Health Service has tended to bend over backwards to avoid unnecessary supervision is worthy of record.

The letters follow:

EDWARDS A. PARK
June 21, 1948

DEAR DR. PARK:

I am glad to answer the questions presented in your letter of June 9th. These answers are, of course, expressions of my personal opinion and do not necessarily reflect the opinion of the faculty which I represent.

I would favor Federal grants for the improvement and expansion of pediatric education if they could be made available without the restrictions sometimes associated with grants from Federal agencies. Improvement in the quality of medical care for children or for any other group will be dependent, to a large degree, upon the type of instruction our physicians receive as medical students, house officers, and practicing physicians. Deficiencies in their instruction in pediatrics in many schools are referable to lack of qualified, salaried teachers and indirectly to inadequacy of the budget for instruction in this field.

Your second question relates to the use which would be made of a grant for pediatric

education if it were received. I shall assume that a grant of fixed amount would be guaranteed for a period of five years and could be used at the discretion of the dean and professor of pediatrics. It would make possible the appointment of a larger number of experienced and well qualified instructors so that our system of instruction in small groups could be further improved and students would receive more individual attention in the wards and out-patient services. Members of a larger staff would have more time free from routine responsibilities for research and study. It would also make possible the payment of more adequate salaries to younger men so that competent physicians would be encouraged to remain in academic medicine.

As you know, there is under consideration provision of Federal funds to cover partial operating expenses of medical schools. Although interested in pediatrics, I am also aware of the needs of other departments in the school. I believe that fluid funds, available for distribution throughout the entire teaching and research budget, could be used more effectively than those which must be designated for the development of individual departments of psychiatry, cancer, pediatrics, etc. Quality of instruction in pediatrics is closely related to availability of good instruction in the basic medical sciences and other clinical fields. Furthermore, in some schools, individual departments are well endowed yet fail to function to greatest advantage because they are not surrounded by equally well-supported units. Perhaps the answer should be more adequate support, through Federal grants, of medical education in general.

Sincerely yours,

(signed) VERNON W. LIPPARD

EDITOR'S NOTE: Dr. Wilbert C. Davison, Duke University, in a letter to Dr. Park dated June 29, 1948, stated that he had seen and thoroughly agreed with Dr. Lippard's letter. He continued as follows:

"I am in favor of a Federal grant for the purpose of improving and expanding pediatric education. If we receive such a grant, we shall increase the size of the pediatric department and also assist with the postgraduate teaching of pediatrics in the surrounding hospitals."

August 18, 1948

DEAR DR. PARK:

Your inquiry concerning my position with regard to receiving federal grants for the improvement and expansion of pediatric education raises a question which should receive our careful consideration. Indeed it is already merging into the larger issue of whether or not federal support should be sought for medical education as a whole.

There is no doubt of the need for additional funds for the teaching of medicine. This has been clearly indicated by a recent statement from authoritative sources. The problem revolves solely around how and where the needed funds should be sought.

To show the nationwide character of the problem, it may be of interest to cite a few of the findings of the Academy study of pediatric education which show the present situation in that field. In 21 of the 70 medical schools, the total amount available to pediatric departments from all sources is less than $10,000 annually. In nine of these schools it is less than $5,000. Three departments have virtually no funds. In addition a number of departments are precariously financed by short term grants. It is a safe assumption that these conditions are not peculiar to pediatrics.

At the present time the federal government makes grants directly to medical schools for purposes of teaching and research under the provisions of the National Cancer Program, the National Mental Health Program, and the National Tuberculosis Program. The eagerness with which these aids are sought does not indicate undue restrictions. On the basis of these facts I can personally see no objection to the extension of federal aid to include the field of pediatrics.

On the other hand, if specific legislation is to be enacted for the support of pediatric or general medical education, great care should be exercised that it should contain no restrictions on university freedom. To this end it would be well if representatives from the educational and general medical fields could participate in its preparation.

The following are items which I think should be included among those designed for the protection of medical education:

1. There should be appointed a National Council with supervisory powers. This Council should include medical educators and members of the medical profession at large as well as representatives of the government services.

2. A large proportion of the annual appropriation should be for current expense with no further restrictions on its use.

3. The number of students to be admitted and their selection should rest entirely with the medical school.

4. The selection of recipients of national scholarships should rest with the National Council. The holders of such scholarships should have free choice of schools and the schools should retain the right to accept or reject the applicants and to dismiss them for due cause.

5. In view of the present shortage of physicians in the government services, it is probable that a law would provide scholarships which include an agreement by the appointee to serve, after graduation in governmental health activities (Army—Navy—Air Force—Public Health Service—Veteran's Administration) or in areas of physician need. This agreement should also permit this service to be rendered through teaching or research in the medical school attended by the appointee, upon request by the faculty of that school. This clause would allow for the retention of students with exceptional qualifications for teaching or research and it is anticipated that it would be invoked but rarely.

As indicated above, the great need is funds for current expense. In the main this means salaries for teachers, research workers and administrative staff. Many able part-time teachers would gladly devote more time to their medical school duties if they were paid a reasonable sum for their services. As it stands at present, they are paid nothing or a mere token and cannot afford to take the additional time from their practice. This single provision would immeasurably improve the situation in many schools.

A budget which would provide salaries for investigators should result in an active research program, with benefits which need not be developed here.

Some departments lack the funds to pay a single full-time secretary. When it is realized that full-time heads of pediatric departments average 60% of their time in administration and usually have reasonable clerical help, the difficulties in the situation faced by part-time heads with no secretarial assistance, can be understood readily. The effect on the teaching program of the administrative disorganization, which sometimes results, is a feature which is not generally accorded its full importance.

In summary I might say, that it is my firm conviction, that most of the ills which plague pediatric education today, stem from lack of funds.

Sincerely yours,

(signed) JOHN McK. MITCHELL

June 16, 1948

MY DEAR DR. PARK:

Here are my personal views in answer to your questions:

The acceptability of federal aid for pediatric education would depend on the manner, conditions, or restrictions which accompanied the subsidy.

(1) With the continued growth of medical science and with the present inflated economy, the costs of maintaining schools of medicine have risen to the point where most schools are having financial strain. Pediatrics is but one segment of the professional discipline and I would much prefer to consider the whole rather than a restricted or limited portion.

(2) There is a strong tendency to link responsibility for extension of medical service with educational programs. While there is inherently an area of service connected with the educational programs in clinical medicine, I believe medical schools can best serve in their primary function of education and research, if they are not forced to accept an extension of service less obviously educational.

For example, there are those who believe that the medical schools should assume a much broader responsibility in the certification program. The present increase in residency training is partly due to government subsidy (G.I. Bill). In the case of selected veteran's hospitals, there have been set up committees to direct the training program for residents and ample funds to meet the costs of the educational program.

For many of the private hospitals, however, the desire for the residency training program is not met by an adequate budget and facilities to provide a training comparable to that given in medical school centers. The impression one gets is that these hospitals are primarily interested in getting the help of good housemen. In such instances, involvement of the medical schools would be equivalent to extending budget and personnel to hospitals not controlled or directed by the schools, for residents not of their selection, and for a professional certificate, not a university degree.

The implied increase of cost would not be confined to the medical schools, but would ultimately be passed on to the consumer: the trainees charging higher fees, thus increasing the cost of medical care.

All of us want to see the best medical service widely distributed within economic practicability. How then is the problem of rural health going to be met? On this, there are two differing ideas:

(1) There should be more emphasis on training the general practitioner. (University of Colorado)

(2) There should be an increased number of specialists.

Both have cogent argument. Both affect the role of medical education. I have already mentioned the costs inherent in specialization. But, with the building of centralized rural hospital facilities, the specialist's role is already weighted, as for example in radiology, pathology, etc. Transportation and communication improvements further weight the role of the specialist. I do believe, however, that at this period of our development, the

profession itself should reaffirm its tradition and help solve the problem. The Boards issuing certification could require a period (after hospital training in a medical center) of rural experience. This would gradually acquaint the profession with the problem and would have a leavening effect on the present differential between rural and urban pediatric programs. And, any corrective measures undertaken by the profession would, I think, prove more effective than that based on legal mandate.

The University of California has a precedent for three types of federal subsidy.

(1) Building facilities and capital expenditures. In the past, these were W.P.A. and P.W.A. programs.

(2) Hospitalization of certain types of chronic or crippling diseases. Usually the subsidy came from a fund allotted and matched by local and state funds.

(3) Research. At the present time many medical schools are enabled to carry on some very important investigations, largely on federal contract. It is, however, true that many of these research programs are technologic, rather than basic and that many schools would prefer a more fluid research subsidy. Some of the programs involve tedious red-tape contracts for obvious utilitarian significance. I must add, however, that pediatrics has not fared so well as other departments in the matter of opportunity for subsidies.

While, of course, I cannot speak for the Regents of the University of California, I believe they would accept subsidy for buildings, for hospitalization costs, and for some research programs. Beyond that, I believe they might be cautious with regard to programs which might dictate curriculum, or threaten independence in the conduct of the school. There is something to be said against stultifying standardization and there is an inherent ineptness in large administrative units.

Sincerely yours,

(signed) FRANCIS SCOTT SMYTH

July 13, 1948

DEAR DR. PARK:

In July 1946 the National Mental Health Act became law as an amendment to the authority given the U. S. Public Health Service. This Act authorized the establishment of an Institute of Mental Health, the granting of funds for research and training and grants to states on a matching basis for preventive activities in the field of mental health. Such funds are not useable for the care of patients in mental hospitals.

While the focus of this Act is psychiatric and the Advisory Council so created is composed largely of psychiatrists, the activities supportable under this Act extend far beyond the customary scope of the psychiatrist. Were this not the case it could hardly be preventive, for the early stages of psychiatric disorders are not found as much in the practice of the psychiatrist as of other physicians. Almost every other specialist and general practitioner encounters psychiatric disorders before they are seen by the psychiatrist.

The early treatment, to say nothing of prevention which must antedate early treatment, calls for increased competence on the part of all physicians and prevention itself lies also within the scope of several non-medical groups, such as teachers, clergymen, social workers and public health personnel.

This Act permits grants to strengthen the preventive competence of all these groups and psychiatrists are more and more inclined to lend their support to the strengthening

of this competence. Recent appointments to chairs of psychiatry in medical schools have recognized the growing theory that the role of psychiatry in undergraduate medical education is not to produce more psychiatrists, but physicians of all sorts who will have knowledge and skill in handling the personal problems and distorted attitudes of all of their patients. They must know anxiety in all its disguises and how to make it work for the patient rather than against him. They must be skilled in talking with a patient so as to use this as a technical resource as powerful and as revealing as gadgets and drugs. They must know the subtle inter-relationships within a family and how they may build up or tear apart a personality; and they must know the resources of a community to help patients and how to use them.

It is the intent of those administering this Act to strengthen both undergraduate and postgraduate medical education so as to accomplish these aims and to see to it that every section of the country has at least one medical school with a strong department of psychiatry focused on these objectives. It has set aside a stipulated number of stipends for training in child psychiatry and there is no reason within the law why a pediatrician concerned to strengthen his competence on the psychiatric side could not be granted a fellowship for this purpose.

As the National Mental Health Act is set up the relation between the U. S. Public Health Service and the educational institution is an entirely voluntary one, but even beyond that acceptance of federal support has not in my experience carried with it in the least any arbitrary control. To be sure there are regulations in which a recipient of support must frame his program, but these regulations have been set up by a panel composed largely of faculty members of educational institutions and actually include some of the recipients. Were I to make any criticism it would be toward the tendency of the Public Health Service to bend over backwards and avoid supervision that is necessary to insure an adequate carrying out of a high quality of work under the program submitted. This puts upon an organization such as the National Committee for Mental Hygiene the task of maintaining a close watch on the operation of such activities in order that it may use whatever resources it has to stop or forestall unwise use of public funds.

The importance of this law to the relatively normal child is evidenced by the fact that the state department through which the state grant aspect of this law operates is, in most cases, the state department of health, which in the past had little psychiatric responsibility. Under these funds the state may select a staff or prospective staff member in the field of child hygiene and place that person in special training in order that the mental hygiene elements may be strengthened.

Sincerely yours,

(signed) GEORGE S. STEVENSON

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

THE CHILDREN'S BUREAU RESEARCH PROGRAM

THE need for research in the field of health and welfare of children may be considered the essential origin of the Children's Bureau. In recent years, however, maternal and child health services, supported by large grants-in-aid to states, have overshadowed the Bureau's research function. The latter is, in fact, relatively unfamiliar except to those immediately concerned. However, at the present time, increasing attention is being given to strengthening and enlarging the Bureau's research program. There is good reason to anticipate that this matter will be brought to the attention of the 81st Congress.

Accordingly, Dr. Bain, Director of the Bureau's Division of Research in Child Development, has been asked to prepare the following statement for publication in this column:

A variety of research studies has been made by the Children's Bureau in the 36 years of its existence, sometimes independently but often in cooperation with institutions already engaged in similar investigations.

In the first decade of its existence the Children's Bureau, in line with its mandate to investigate and report "upon all matters pertaining to the welfare of children and child life among all classes of our people," concentrated its small resources on studies of conditions surrounding the lives of children. A series of community studies on infant mortality revealed the social and economic factors associated with a high mortality rate. As a result of these studies, services were developed, both within and without the federal government, that have helped in reducing deaths in infancy. The Children's Bureau has no authority, or funds, for grants for research. But cooperative arrangements have proved a useful technic for assisting research in which the Bureau had a special interest but for which its finances were insufficient. Examples of such assistance rendered by the Children's Bureau are: The analysis of feeding records of premature infants at New Haven Hospital under Dr. Powers; work on the physiology and care of premature infants at the New York Hospital under Dr. Levine and Dr. Gordon; and work on rickets at Johns Hopkins with Dr. Park. The Academy Study of Child Health Services is a recent instance of cooperation in research through the loan of personnel.

When, in 1935, the Children's Bureau was given responsibility for administration of grant-in-aid programs for services under the Social Security Act, its research activities were overshadowed by the pressures of an expanding administrative program. What little research survived the increase in "service programs" was finally lost in the general curtailment of all work not directly related to the war.

Since the war the Children's Bureau has given serious consideration to its research

program. In doing this it attempted to learn what research programs were in progress and what others were needed in the total field of child life.

The National Health Assembly through the Maternal and Child Health section has made the following statement about these problems:

"Ever increasing funds are being spent for services to people, with little or no increase for the investigation of the basic problems which produce the needs for service. Premature birth is the major cause of death in infancy. The care necessary to save the prematurely born infant is expensive, often running into hundreds or thousands of dollars per individual. Compared to the cost of care, the amount expended on research into the causes of prematurity is insignificant. The situation is the same for other diseases, such as cerebral palsy, rheumatic fever, and congenital defects.

"In the social field the same disproportion exists. Effort and money are expended in caring for the end results of a problem—the emotionally ill, the socially maladjusted, the delinquents—with neglect of research into the basic causes underlying the problems.

"Just as child health is no longer considered entirely the result of medical care but the product of endeavor by many professional and nonprofessional disciplines, so research in child health has been broadened to include many fields which may better be grouped under the term "child life." The interaction of a child and his environment is so complex that research into almost any of his problems must have a multi-disciplined approach. What appears on the surface to be a simple physical problem, such as inability or failure of mothers to breast-feed infants, needs a combined attack from the field of medicine, psychology, anthropology, economics, and others."

As a first step in reviewing the problem of research in the broad field of child life, the Children's Bureau called a series of small advisory conferences. The first of these, held in New York in November 1947, consisted of 16 outstanding investigators from a variety of fields: pediatrics, psychology, anthropology, psychiatry, education, sociology, and so forth.

This conference discussed such questions as: What research in child life is now going on, inside and outside the federal government? On what aspects of child growth and development, and of community life in relation to children, is research most needed? What are the major obstacles in the way of research? What next steps should be taken? What contributions can the Children's Bureau make?

As a result of its deliberation the conference recommended that an information center on research in progress should be established as a first step toward implementing research in the field, in order that members in one scientific discipline might know of related investigations being made by other disciplines.

Acting on this recommendation the Children's Bureau is in the process of setting up a Clearing House on Research in Child Life in the Division of Research in Child Development of which Dr. Katherine Bain is Director. It will be organized and operated by a new member of the Children's Bureau staff, Dr. Clara Councell, who comes to the Bureau from the Medical Division of the Institute of Inter-American Affairs, an agency of the State Department. A small technical advisory committee to the Clearing House has been appointed by the Bureau to assist in the establishment of technics and procedures. Obviously some months must elapse before a project of this scope can be operating fully.

Two other small research conferences were held in 1948 to consider the areas most in

need of investigation, and ways of furthering such research. Further conferences are planned for the fall and winter of 1948-1949.

Another recommendation of the advisory groups was that the Children's Bureau have a permanent research advisory committee, and the Bureau has asked the National Research Council for assistance in this. As a result the Committee on Child Development of the National Research Council, a committee of long standing, has been reorganized to serve in an advisory capacity to the Children's Bureau as a part of a large research advisory committee. The new committee of the National Research Council is constituted as follows:

Dr. Robert R. Sears, Director, Iowa Child Welfare Research Station, State University of Iowa, Iowa City, Iowa, Chairman.

Alfred Washburn, M.D., Director, Child Research Council, University of Colorado School of Medicine, Denver, Colo., and President of the Society for Research in Child Development.

Clyde Kluckhohn, Ph.D., Department of Social Relations, Harvard University, Cambridge, Mass. (anthropologist)

Sibylle Escalona, Ph.D., Menninger Foundation, Topeka, Kan. (child psychologist)

Samuel Z. Levine, M.D., Professor of Pediatrics, Cornell University School of Medicine, and Director, Children's Clinic, New York Hospital, New York, N.Y.

Allison Davis, Ph.D., College of Education, University of Chicago, Chicago, Ill. (sociologist)

Katherine Bain, M.D., Director of Division of Research in Child Development, Children's Bureau, Federal Security Agency, Washington, D.C.

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

THE PLASMA PROTEINS: THEIR FUNCTIONS AND CLINICAL USES

By CHARLES A. JANEWAY, M.D.

THE subject of this lecture is a field in which knowledge has accumulated very rapidly in the last few years. The reasons for these rapid advances are manifold, but first among them is the fact that during the war, blood, the raw material for research, was made available in adequate amounts for study by donors of the nation through the Red Cross Army-Navy blood program. Second, the stimulus of war led to the large scale application to the fractionation of plasma of the methods of protein chemistry which had been developed meticulously over a period of years in laboratories in Scandinavia, England, and the United States. Finally, a pattern developed during the war under government auspices, which is now being continued under the leadership of the American Red Cross, whereby plasma protein fractions were made available to interested investigators so as to return to our people, who gave their blood voluntarily, as many benefits as possible from the therapeutic and preventive use of blood derivatives and from a better understanding of human physiology. This lecture will attempt to summarize the present state of our knowledge in this field. For purposes of brevity, it will be impossible to mention every individual who has made an important contribution, but it should be pointed out that this is a summary of the work of a large group of investigators—chemists, immunologists, pathologists, physiologists, pharmacologists, and clinicians—to whom the author acknowledges his debt of gratitude.

THE PLASMA PROTEINS

Plasma is the fluid matrix in which the cellular elements of the blood are suspended and transported about the vascular system. It differs from the interstitial fluids with which it is in osmotic equilibrium by its higher content of proteins. These plasma proteins consist of a complex mixture of multiple components (over 60 different physiologic components have been identified in plasma already) differing in their source, fate within the body, chemical structure, and consequent physiologic function. Moreover, the plasma proteins, present in 7% concentration in approximately 7% of the body water, are in a state of equilibrium with the large pool of proteins of the body tissues, present in concentrations of 20-30% in 72% of the body water. Between these two depots of body protein—the plasma proteins and the cellular proteins—stand the interstitial fluids representing about 21% of body water. The plasma proteins pass into these fluids in extremely low concentrations, if at all, through the choroid plexus and the ciliary processes,

From the Department of Pediatrics, Harvard Medical School and the Children's Medical Center, Boston, Mass.

Delivered at the 13th Annual Leo Loeb Lecture, March 19, 1948 at Washington University School of Medicine, St. Louis, Mo., under auspices of Mu Chapter, Phi Beta Pi fraternity.

Slightly revised and reprinted with permission from the Washington University Alumnæ Quarterly and the Phi Beta Pi Fraternity Quarterly.

where the capillaries are covered by one or more layers of cells, in relatively low concentrations (from 0.1—0.3%) into the interstitial fluids of the extremities where the concentration has been measured, but probably in higher concentrations in liver, spleen, lymph nodes, and bone marrow where a sinusoidal structure predominates. There is no direct information available on this point, but the high protein content of lymph collected from lymphatics, particularly within the abdominal cavity, which return protein from the tissues to the blood stream, is suggestive.

The importance of the liver in the production of certain plasma proteins is established very firmly. Serum albumin, serum esterase, prothrombin, and fibrinogen are all known to be derived from the liver, and their concentrations reflect the functional capacity of that organ except when other factors, such as malnutrition, plasma loss, or vitamin K deficiency, are present. The probable importance of the lymph follicles in the synthesis of serum gamma globulin and the antibodies associated with this fraction has recently been appreciated as a result of the work of White, Dougherty, Harris, and others. The derivation of many of the trace components of plasma—hormones, vitamins, enzymes—has been suggested by their behavior in disease. Thus the high serum amylase values found in mumps parotitis or in acute pancreatitis clearly point to the salivary glands and pancreas as the probable source of the traces of amylase normally found in the plasma. Fractionation of plasma and consequent concentration of components in specific fractions has led to the identification of a number of components in plasma, such as the thyrotropic hormone, normally present in too small amounts in plasma for demonstration with available technics.

Little is known of the factors which control the rate of production of different plasma proteins so as to maintain a balance between various components. The role of vitamin K in the synthesis of prothrombin by the liver and the action of antigens in initiating the production of specific gamma globulin antibodies by the lymphoid tissues are two examples of known stimuli which enhance the production of individual plasma proteins.

The function of the plasma proteins in maintaining the volume of circulating plasma is somewhat better understood; at least, little evidence has yet been adduced to upset the fundamental validity of Starling's hypothesis that the oncotic pressure of the plasma proteins normally balances the filtration pressure exerted through the capillary wall, so as to maintain a relatively constant volume of circulating plasma. Recent studies have shown that this can be displaced markedly by the administration of large amounts of serum albumin or of sodium salts, the latter producing a marked expansion of total extracellular fluid. In conditions where the plasma oncotic pressure is greatly diminished, a marked decrease of the circulating plasma volume is probably prevented by high tissues fluid pressure due to stretching of the skin by the generalized edema, which tends to balance the filtration pressure.

A major advance in our knowledge of the plasma proteins has come from the development during the war of methods, based on the accumulated theoretical studies of protein chemists, for the large-scale separation of these proteins into fractions for therapeutic use. Such methods, unlike those in previous use in the serum industry, must be inclusive; that is, they should make it possible to recover all physiologically active components in the final fractions, not just one, as for example in the separation of pneumococcus antibody from hyperimmune horse serum. Moreover, the methods must be capable of application on an industrial scale at low cost, and must give rise not only to undenatured protein, but

to protein preparations which can be injected in large doses without harmful reactions. The methods developed by Prof. Edwin J. Cohn and his colleagues at the Harvard Medical School have met these criteria and are beginning to have widespread application in the biologics and pharmaceutical industry wherever the basic problem is the separation of specific proteins from mixtures. Not only the fractionation of plasma, but the purification of toxoids, the concentration of viruses for vaccines, and the separation of hormones from organ extracts has been improved by this development. The new principles on which these methods are based are: first, the employment of volatile organic solvents as precipitants; and, second, the use of a five variable system in which temperature, pH, and concentration of precipitant, of protein, and of ions can be varied in order to develop conditions most suitable for the separation of each fraction. The use of an organic solvent (ethanol in the plasma fractionation methods) does away with the clumsy dialysis procedure necessary if neutral salts are used to precipitate the protein, since it can be removed from the precipitate by drying from the frozen state. It also makes it possible to operate the whole procedure below the freezing point of water, thus minimizing the chance of protein denaturation or of the growth of contaminating bacteria. By separation of the plasma proteins into different fractions, conditions most suitable for the preservation of each active component can be developed, thus avoiding waste of valuable blood and permitting the storage of various components until they are needed.

Details of the procedures for plasma fractionation are undergoing continuous modification as knowledge advances. These methods are of such a nature that the same number of chemists can handle the fractionation of 10,000 bleedings as easily as 200, provided suitable large scale equipment is available. Thus, for economical operation, they should be carried out on a large scale. This is one of the strongest arguments in favor of a national blood program, such as is planned by the American Red Cross; otherwise, collection of blood will not be done on a sufficiently large scale to make fractionation economically feasible.

The method now in use leads to an initial division of the plasma proteins into five fractions, several of which must be subjected to further fractionation for purification of their important physiologic constituents. (See Table I).

Perhaps the most important outgrowth of the purification of the plasma proteins in sufficient amounts to permit both physiologic and chemical studies with the same material is the insight which it is giving us into the relation between the chemical structure of the protein molecule and its function. This chemical-anatomic study of an important body tissue is only the beginning of a series of investigations which it is hoped may ultimately reveal the molecular forces at work in the body. Only two of the plasma proteins have been prepared in crystalline form—serum albumin and the β_1—metal combining protein—although fibrinogen, gamma globulins, β_1-lipoproteins and α-lipoproteins have been prepared in sufficient purity to provide a good picture of their general molecular characteristics. These studies have revealed an extraordinary diversity among the plasma proteins. Thus serum albumin has a molecular weight of 69,000, an elliptical shape, and a high net charge, fibrinogen has a molecular weight of 500,000, a needlelike shape, with consequent viscosity in solution, and a low net charge, while β_1-lipoprotein has a molecular weight of over one million, a round symmetrical molecule, and a structure into which 75% of lipoid is incorporated in water-soluble form. These differences are also reflected in their content of the different amino acids. Such studies begin to make

the abnormalities of the plasma proteins in disease more intelligible and lead to a far better understanding of the properties of the different proteins in solution: their viscosity, solubility, and osmotic effects.

The reasons for feeling that the fractionation of human plasma is sufficiently worth-

TABLE I

FRACTIONS OF NORMAL HUMAN PLASMA

Fraction	% of Plasma Proteins	Major Chemical Components	Major Physical Constituents	Subfractions	Major Chemical Components	Major Physiologic Constituents
I	5	Fibrinogen (65%)	Fibrinogen Antihemophilic Globulins			
II and III	29	β_1-, β_2-, γ-Globulins		III-0	β_1-lipoproteins*	X-Protein
				III-1	β- and γ-Globulins	Isohemagglutinins
				III-2	β_2-Globulins	Prothrombin
				III-3	β_1-, and γ-Globulins Fibrinogen	Plasminogen
				II	γ-Globulins (95%)	Antibodies
IV-1	8	α_1-lipoproteins*				
IV-4	9	α_2, β_1-globulins		IV-6	α_2- and β_1-globulins	Glycoprotein Serum esterase
				IV-7	β_1-Globulin	Metal-binding protein
V	48	Albumin (98%)	Serum albumin			

* Knowledge of the lipoproteins which comprise approximately 25% of the proteins of normal pooled fasting human plasma is still in its infancy. It is known that these fractions contain steroid hormones, vitamin A, cholesterol, phospholipids in combination with protein in a definite molecular structure.

while, apart from the scientific information so obtained, to justify its continuation as an essential part of any complete blood program deserve documentation. Fractionation makes it possible both to concentrate a specific activity for therapeutic use and to preserve it in a stable state. This is a tremendous convenience to the physician. In the case of gamma globulin, the injection of 2 cc. from a vial in his bag to prevent measles in a baby, a very simple procedure, is the equivalent of a transfusion of 50 cc. of pooled plasma, a relatively major and inconvenient operation. Moreover, there is an element of

safety, in that homologous serum jaundice has not been observed after the injection of gamma globulin; whereas, it follows the use of pooled plasma in approximately 4 to 5% of cases. The factor of concentration makes it possible to transfuse amounts of substances such as fibrinogen that would not be possible with whole blood or plasma. The use of specific proteins for specific purposes is not only more effective, but more economical of blood, since, after fractionation, the donation of a single individual may be involved in the treatment of a considerable number of patients.

Clinical Use of Plasma Fractionation Products

A. *Proteins Concerned with Coagulation:*

The complexities of the coagulation mechanism are far from solved. Most of the important coagulation factors circulate in the form of inactive precursors which are converted to the active form by a chain of events which leads through a series of steps to the formation of a clot, and then to its ultimate lysis. Because conversion apparently takes place at a slow rate even in the circulation, a series of antagonists, such as antithrombin, likewise circulate in low concentration, preventing intravascular coagulation under normal conditions.

The matrix of the blood clot is provided by fibrinogen, the long needle-like molecules of which are polymerized to a system of tangled fibrils by the action of thrombin in the process of coagulation. Fibrinogen is available for clinical use in Fraction I, which contains between 60 and 70% fibrinogen, and a mixture of other globulins, among which is found "the antihemophilic globulin." The nature of this substance is not known. It is not fibrinogen, but has not been concentrated in a fibrinogen-free fraction. It is highly unstable, losing activity very rapidly when plasma stands in contact with cells and fairly rapidly in plasma alone. Prothrombin, the precursor of thrombin, to which it is converted by the action of a tissue extract, thromboplastin, in the presence of Ca^{++} ions, is found in Fraction III-2 which contains predominantly β_2-globulins. So far it has not been possible to stabilize prothrombin sufficiently to justify its distribution for therapeutic injection, since the danger of its spontaneous conversion to thrombin is too great. A fourth protein of importance in coagulation is plasminogen, the precursor of plasmin, the proteolytic enzyme of plasma, to which it is converted spontaneously, at a slow rate, but rapidly by an activator, streptokinase, produced by group A beta hemolytic streptococci. This activation of a plasma enzyme by this organism accounts for its well-known fibrinolytic activity. This enzyme not only will dissolve preformed clots but will also destroy the coagulability of fibrinogen solutions.

Fraction I has been used in the replacement therapy of two diseases—hemophilia and afibrinogenemia. The intravenous injection of from 200 to 600 mg. of Fraction I will lower the coagulation time of most hemophiliacs to within normal limits. It has been used as a convenient method for controlling hemorrhagic episodes and in preparing patients for dental and surgical procedures. The effect of a single injection only lasts for roughly 8 to 12 hours, hence must be repeated frequently. Recent reports of the appearance of anticoagulants in the blood of certain hemophiliac patients after repeated transfusions of blood or injections of Fraction I require further investigation.

In afbrinogenemia, a rare clinical condition, the high concentration of fibrinogen in Fraction I makes it possible to bring a patient's circulating fibrinogen from zero to normal

levels, something which would be absolutely impossible with bloods or plasma without a complete replacement transfusion.

Fibrinogen has been used with thrombin as a sort of physiologic glue to promote the adherence of skin grafts. By clotting fibrinogen with thrombin under controlled conditions, it has been possible to develop products of human protein which have the great virtue of eliciting minimal tissue reactions when left in situ at operations. Fibrin foam, a sponge which, when soaked in a solution of thrombin, serves as a very effective hemostatic agent, has been of great value in neurosurgery, particularly in the control of bleeding from the major dural sinuses in war wounds. Fibrin film, a transparent pliable membrane of fibrin, can be used as a replacement for the dura mater and will serve as a bridge across which a new membrane will grow without the formation of adhesions and consequent neurologic sequellae.

B. *Antibodies to Infectious Agents:*

Quantitative recovery of those antibodies present in pooled human plasma has been obtained in Fraction II and III, in which, however, gamma globulins only comprise about ⅓ of the protein. Further purification leads to a 25 fold concentration of these antibodies in Fraction II, which contains 95% gamma globulin, with a yield of 55% in the original method and about 75 to 80% in the final modification.

Solutions of concentrated gamma globulin from pooled normal plasma might be expected to protect susceptibles passively against those diseases to which the infant is not susceptible in the early months of life and to be ineffective in the prevention of those diseases which the infant readily contacts in early life. This prediction has been borne out where it has been studied, with one clear-cut exception, epidemic parotitis. Injections of concentrated gamma globulin do not protect susceptible children against either varicella or epidemic infantile diarrhea. On the other hand, gamma globulin, injected into susceptible children after exposure, has been shown to exert a protective action against both measles and infectious hepatitis. Careful studies throughout this country over a period of several years have established the reliability and safety of gamma globulin in the control of measles. Doses of at least 0.2 cc./kg. of body weight administered within the first week after exposure will protect the great majority of children completely against the disease. This has led us to abandon quarantine of a ward where measles breaks out in the hospital. Doses of one-fifth this amount (.04 cc./kg.) administered in the same period after exposure lead to modification of the disease in most children and only prevent its occurrence in 5 to 10% of the patients. This reliability makes routine use of this preparation possible for active immunization of exposed children. Over a million doses of gamma globulin have been distributed by the Red Cross for this purpose.

In the case of epidemic parotitis it has been demonstrated that one factor in the failure of normal serum gamma globulin to protect against the disease may be a deficiency in the quantity of antibody present. When a gamma globulin preparation derived from convalescent mumps plasma was compared with normal serum gamma globulin in the treatment of mumps parotitis in an outbreak at an Army Camp, the incidence of complicating orchitis was markedly reduced in the group receiving convalescent material, but not in the other group. The possibility of using antibody preparations derived from convalescent plasma in the handling of certain diseases where high levels of antibody develop is something which deserves further study under the Red Cross.

One mystery about normal serum gamma globulin which has defied explanation is its toxicity on intravenous injection. Although reactions have been practically nonexistent on intramuscular injection for measles prophylaxis, intravenous injection of the most highly purified preparations into normals in moderate doses and into patients ill with acute infections in much smaller doses has led to acute vasomotor reactions followed by severe chills and hyperpyrexia. This has occurred so regularly that one wonders whether it has genuine physiologic significance.

C. *Blood Grouping Globulins:*

Since whole blood is used more than any of its derivatives, the necessity for potent, accurate, and well standardized blood grouping reagents is obvious. Present practices in this regard, although practical, are none too satisfactory. When plasma from donors of a single blood group is used for fractionation, it is possible to concentrate in Fraction III-1 the isohemagglutinins for erythrocytes of the incompatible groups. Group A bloods, comprising slightly over 40% of all donations, yield satisfactory anti-B agglutinins. Group B bloods occur with much less frequency, and it has been shown that a better anti-A agglutinin preparation can be made by fractionation of the common group O blood and absorption of its anti-B agglutinins with group B cells. Anti-Rh preparations can similarly be prepared from pools of anti-Rh plasma obtained after pregnancy or incompatible transfusions. When the cells to be tested are suspended in albumin solution to inhibit the effect of "blocking antibodies" these anti-Rh globulins give excellent agglutination. Although isoagglutinin preparations of this type have not yet been widely used they have the virtues of ready standardization, packaging in stable form, easy production as a by-product of a blood program, and the availability of highly potent blood grouping material without the necessity for titration of the serum of each donor until a suitably potent one is found.

D. *Normal Human Serum Albumin (Salt-poor):*

Half of the plasma protein is recovered as 98% pure albumin in Fraction V. As now distributed this preparation consists of a 25% solution of normal human serum albumin in a diluent buffered to pH 6.8, containing approximately one-seventh as much sodium as an osmotically equivalent volume of citrated plasma and 1% acetyl tryptophanate as a stabilizing agent. This solution is heated 10 hours at 60°C in the final container, a procedure which seems to inactivate the virus of homologous serum hepatitis, and which has made it possible to omit the mercurial preservatives which are still used in plasma under ruling of the National Institute of Health.

During the war, the usefulness and safety of serum albumin as an emergency blood substitute was clearly demonstrated. In cases of shock with adequate hydration each gram of albumin can be expected to add approximately 17 cc. of fluid to the circulation within an hour, which is close to the amount predicted by osmotic pressure measurements in vitro. On the other hand, in severe shock, with dehydration, the average is only 12 cc. and marked variation in response may occur. Hence albumin should be followed by additional fluids (saline 400 cc./25 gm. to give a solution isosmotic with plasma) in shock cases whenever possible. The convenience, compactness, ease of administration, and safety of albumin make it preferable to plasma in most instances as an emergency blood substitute.

The use of albumin in the treatment of hypoproteinemia is under active investigation

today, and hence much of what is recorded here may have to be revised when more data is available. The causes of hypoproteinemia are multiple; in most instances, particularly where edema is a prominent symptom, there is principally a reduction in the amount of circulating albumin. This may come about as a result of plasma loss, massive proteinuria, or the catabolism of protein in infections with inadequate caloric and nitrogen intake to meet the drain on body reserves, or as a result of inadequate albumin synthesis, due to hepatic insufficiency. In hypoproteinemia, albumin has been used to correct a major physiologic disturbance, edema, although the extent to which failure of certain functions other than the osmotic one—such as the binding and transport of small molecules, interaction with plasma and tissue proteins—play a role in hypoalbuminemic patients has never been assessed.

The importance of an adequate protein and caloric intake for the repair of body protein deficits cannot be over-emphasized; it is most properly met by oral feeding, but parenteral alimentation with protein hydrolysates and dextrose solutions may be a useful supplement in those cases where an adequate intake by mouth is impossible. The place of serum albumin in the treatment of nutritional hypoproteinemia would seem to be in those cases where one cannot afford to wait for the relatively slow formation of serum albumin in response to food. This is a situation met relatively frequently in the surgical wards, as for example, when a patient must be operated on promptly to relieve intestinal obstruction or when edema develops at the stoma of an anastomosis of two portions of the gastrointestinal tract. In cases of burns, exfoliative dermatitis, and severe diarrhea frequently the protein loss is so rapid that it can only be met with injections of preformed protein, particularly since there is apt to be increased protein breakdown and nitrogen loss under these circumstances.

A second set of conditions under which serum albumin should be useful is in cases of hepatic disease where the actual synthesis of this protein is impaired even in the face of a strongly positive nitrogen balance. Cirrhosis of the liver has been divided into three main types, biliary cirrhosis, the rare coarsely nodular cirrhosis secondary to the progression of an infectious hepatitis, and the finely granular Laennec's type of cirrhosis. Demonstration that lasting remissions in some cases of the latter group can be produced by prolonged dietary therapy makes an even stronger case for relieving their disabling edema if possible with albumin during the course of dietary therapy. It has been possible to relieve edema and ascites in some cases of post-infectious cirrhosis, but the administration of albumin apparently has no influence on the course of the underlying hepatitis. In early instances of Laennec's cirrhosis a diuresis will occur after a period of dietary therapy alone, although albumin administration may hasten it; whereas, in advanced cases, although albumin administration leads to elevation of the serum albumin concentration, there is often a concomitant rise in the concentration of albumin in the ascitic fluid and failure to deliver the ascites.

No aspect of albumin therapy has been subject to greater misunderstanding than its place in the treatment of the nephrotic syndrome. The administration of serum albumin to patients with nephrosis has proved conclusively that the nephrotic kidney is unable to retain normal serum albumin. This puts the burden of proof on those who say that the primary defect in this disease is a production of abnormal albumin rather than a change in the kidney itself. Prolonged albumin therapy leads to a slow diuresis in many of these patients, to very slight increases in plasma albumin concentration, and to massive pro-

teinuria which accounts for a large portion of the injected protein. The benefits of diuresis are transitory in most patients. A serious problem requiring further investigation is to what extent this marked increase in proteinuria is harmful to the kidney per se. Some patients have shown hematuria during the course of injections. Thus albumin must be considered a symptomatic remedy to be used with caution in a disease, the fundamental nature of which remains obscure.

There are many other potential uses of albumin under investigation. It is a physiologic hyperosmotic solution which may be useful in the reduction of local edema, particularly within the cranial cavity. It has been a very useful tool in physiologic research upon shock, cardiac failure, renal function, the control of water balance in various types of edema, the control of the level of protein-bound iodine of the serum, and the control of calcium and phosphorus balances in osteoporosis.

Summary

This brief review of some of the recent accessions to our knowledge of the chemical structure, physiologic functions, and therapeutic applications of the plasma proteins serves to emphasize three important elements in medical progress—scientific curiosity, the humanitarian impulse, and effective social organization. We have had the privilege of summarizing the work of hundreds of investigators, whose studies are giving us new tools for the investigation and treatment of disease. Their work has only been possible because the magnificent response of a free people to the call for blood donors by a voluntary philanthropic agency, the American Red Cross, was coupled with a technical triumph, the development of practical methods for the large-scale separation of the plasma proteins, itself the culmination of highly theoretical and seemingly impractical investigations by protein chemists in various countries for many years.

References

1. Cohn, E. J., Onkley, J. L., Strong, L. E., Hughes, W. L., Jr., and Armstrong, S. H., Jr., Chemical, clinical and immunological studies on products of human plasma fractionation of protein fractions of human plasma, J. Clin. Investigation **23**:417, 1944.
2. Hegsted, D. M., Hay, Alice L., and Stare, F. J., Chemical, clinical and immunological studies on products of human plasma fractionation; studies on nutritive value of human plasma fractions, J. Clin. Investigation **24**:657, 1945.
3. Taylor, F. H. L., Davidson, C. S., Tagnon, H. J., Adams, M. A., MacDonald, A. H., and Minot, G. R., Studies in blood coagulation; coagulation properties of certain globulin fractions of normal human plasma in vitro, J. Clin. Investigation **24**:698, 1945.
4. Cameron, J. W., and Diamond, L. K., Chemical, clinical and immunological studies on products of human plasma fractionation; serum albumin as a diluent for Rh typing reagents, J. Clin. Investigation **24**:793, 1945.
5. Thorn, G. W., Armstrong, S. H., Jr., and Davenport, V. D., Chemical, clinical and immunological studies on products of human plasma fractionation; use of salt-poor concentrated human serum albumin solution in treatment of hepatic cirrhosis, J. Clin. Investigation **25**:304, 1946.
6. Cohn, E. J., Separation of blood into fractions of therapeutic value, Ann. Int. Med. **26**:341, 1947.
7. Cohn, E. J., Chemical, physiological and immunological properties and clinical uses of blood derivatives, Experientia **3**:125, 1947.

NEWS AND ANNOUNCEMENTS

Announcement has been made by the American Academy of Pediatrics of receipt of a three-year grant of $50,000 from the National Foundation for Infantile Paralysis. The fund will be used in support of the continuing program of the Academy's Committee for the Improvement of Child Health directed toward better and more evenly distributed medical care for children throughout the nation—state by state and county by county.

The Committee for Improvement of Child Health will translate into terms of effective action the findings of the two-and-a-half year Study of Child Health Services just completed by the Academy. Financed in part by previous grants from the Foundation and its county chapters, the Study has determined just what services are available to children from the physicians, dentists, hospitals, and community health agencies in every part of the nation. Also included was an evaluation of pediatric education in all medical schools.

Pilot state for the nation-wide study was North Carolina, in which polio has this summer reached epidemic proportions. Although marked gains have been made in recent years for improving medical care of children, the findings in this state alone disclosed that only 13 of the state's 113 general hospitals of 25 or more beds treat children with acute polio. The rate of care in clinics for physically handicapped children in the state is only a third of that in a more favored state, the study revealed. Close cooperation with state health departments and medical and health organizations toward developing improved medical services and their better distribution to children of isolated communities will be sought under the Academy's action program.

* * *

Columbia University College of Physicians and Surgeons and the Neurological Institute of New York City are cooperating with the University of Texas Medical Branch, Galveston, in a special study of poliomyelitis. Also working with the group is Baylor University College of Medicine, Houston, with Dr. Paul R. Harrington, associate professor of orthopedic surgery, participating.

The investigation plans to devise criteria for evaluating the neuromuscular status of poliomyelitis in patients. Clinical chemotherapeutic studies will be made with special reference to antibiotics and synthetic compounds which have been shown experimentally to have value against the virus of poliomyelitis.

The cooperative research is under the direction of Dr. Murray Sanders, associate professor of bacteriology of the College of Physicians and Surgeons, Dr. Clifford G. Grulee, Jr., assistant professor of pediatrics and director of the poliomyelitis unit of the University of Texas Medical Branch, and Dr. Saul R. Korey of the Neurological Institute, New York.

* * *

The University of Colorado School of Medicine and the Colorado State Department of Health announce a short course for physicians on problems of new born infants to be given at the University of Colorado Medical Center, Denver, October 14 to 16, 1948.

Lectures, panel discussions and demonstrations will be given by members of the faculty on subjects such as: obstetric aspects of prematurity, resuscitation, isoimmunization, psychologic problems developing in prematurely born infants, community planning, interpretation of laboratory findings in the newborn, and parenteral fluid therapy. The course is open to graduates of Class A medical schools; registration fee is $10.00. Write Frode Jensen, M.D., Director of Graduate and Postgraduate Education, University of Colorado Medical Center, Denver, Colo.

* * *

Five of the top officials in the New York City Department of Health have taken over new positions in accordance with reorganization plans for streamlining the department. Among them is Academy member, Dr. Leona Baumgartner, director of the Bureau of Child Hygiene since 1941, who, as assistant commissioner, will be in charge of the Maternal and Child Health Services Division.

* * *

Dr. Harvey F. Garrison, Jackson, Miss., who is Academy Liaison Officer to the AMA, was the winner of a 1948 Cadillac club coupé presented by White Laboratories, Inc., pharmaceutical manufacturers, at the AMA Annual Meeting in Chicago. Dr. and Mrs. Garrison cancelled their train reservations to drive home in style in their new Cadillac.

INTERNATIONAL NEWS AND REPORTS

FIRST WORLD HEALTH ASSEMBLY

The First World Health Assembly convened in Geneva, Switzerland, on June 24, 1948, and remained in session until July 24. Fifty-four nations sent delegates. The work of this First Assembly centered around the development of a program of action for the World Health Organization. After discussions of a long list of possible activities, the Assembly adopted a program which established certain priorities for the work of the Organization during the coming year. Malaria control, maternal and child health, tuberculosis and venereal disease control, nutrition and environmental sanitation were placed in the top priority. To carry out these priority programs the WHO authorized the appointment of expert committees and the establishment of appropriate sections of work in the secretariat of the Organization.

It was decided early that to be effective WHO must focus its attention on the high incidence of preventable deaths among infants and mothers in large areas of the world; the effectiveness of avalable technics in reducing mortality and in improving the health of children; the immediate and continuing need of scientific guidance in the use of foodstuffs for the protection of the health of children; the high incidence of communicable and other preventable diseases among children; the widespread mental and emotional maladjustments and insecurity among children and youth; the insufficient understanding and knowledge among parents and others of the causes of ill health and abnormal behavior in children; and the effects of economic and social changes on the physical, mental, and emotional development of children.

The objectives of the maternal and child health program are "to assist governments in developing services and facilities that will assure adequate maternity care, the best possible chance of survival to infants, and, to all children, normal physical growth and development, mental and emotional health and freedom from preventable disease; to pool knowledge, acquire new facts, develop standards of care, and distribute information in respect of all relevant matters; and to cooperate with other agencies on joint undertakings which apply knowledge and technics in the fields of social and biological sciences and of education to problems of maternity and childhood."

This is a broad and comprehensive mandate, one that, if properly implemented, would make possible a vast improvement in the health and welfare of mothers and children in many lands. As a beginning, the first World Health Assembly recommended that a program of investigation, study, and assistance to governments be initiated, that a section on maternal and child health be established as part of the secretariat of WHO, that an expert committee on maternal and child health be appointed to advise WHO, with a panel of corresponding members, and that individuals and teams of experts be employed as required.

Specifically it was recommended that studies be made on the causes and methods of reducing maternal, infant, and childhood morbidity and mortality; on the guidance of mental health of children; on the social aspects of a maternal and child health program; and on the facilities and personnel needed to provide maternity care and health services for children, including hospital and auxiliary services.

The program calls for the provision of experts to advise governments on the administration of maternal and child health programs, experts or teams to demonstrate special services; the granting of fellowships to students for post-graduate study; and for making available visiting experts to aid in training.

A part of the function of the maternal and child health section of the secretariat will be to collect and distribute on an international basis information on the health of children, including the results of research and current procedures, methods, and administrative practices; and to prepare special reports on standard technics, methods, and practices in maternity and child care and materials for use in health education programs.

The delegation from the United States included: Thomas Parran, M.D., Medical Director, Public Health Service, Federal Security Agency; Martha M. Eliot, M.D., Associate Chief, Children's Bureau, Federal Security Agency; J. R. Miller, M.D., Trustee, American Medical Association, Hartford, Conn.

MARTHA M. ELIOT, M.D.

PAEDIATRIC SERVICES UNDER THE BRITISH HEALTH ACT

The shape of the paediatric services under the National Health Act will not be properly seen for some time. Nevertheless it is possible to predict the probable way in which they may be organized. It must be remembered that each of the Regions into which England and Wales are divided, based on a University medical school centre, with four for the London area, is free to develop its plans within wide limits and it is unlikely that each regional plan will be exactly the same as the others. Geographical and population differences and the staff available must make for big differences. It is essential that there should be a fully staffed paediatric department in every Regional Centre. Already a University Institute or Department of Child Health with a Professor exists in most of the Regions. Every Hospital Centre outside the University town, that is in major cities without a University, will have a paediatric department and in smaller towns a visiting paediatrician will supervise the work of the children's unit in the hospital. It has been estimated that, excluding beds for infectious diseases and for long-stay cases (i.e. orthopedic and rheumatic), a minimum of one child's bed for every 2,000 of the general population will be required. It has also been estimated that the equivalent of six to eight whole-time paediatricians will be necessary for every million of the population for hospital work and correspondingly more if they are part-time in their hospital services. Taking a standard town of about 100,000 to 120,000 population this will mean about 50 children's beds with the services of one half-time paediatrician and a whole-time assistant of the "registrar" type. It is hoped that paediatricians will be more closely associated than in the past with infectious disease hospitals and also have responsibility for all infants in maternity units.

The relation it is hoped to develop between the hospital services and the preventive services of the local health and education authorities has already been described in a circular published last year. Up to now under the Maternity and Child Welfare schemes a medical officer has usually been expected to cover both the ante-natal side of obstetric work and the child health side of the welfare centre work. In the future authorities are advised to separate these functions. It is suggetsed that selected medical officers with experience and aptitude should be encouraged to specialize in the child health work, perhaps doing some work with the school children as well as in infant welfare centres, and also given facilities to take part in the hospital work of the area. Similarly paediatricians working in hospitals are to be encouraged to become associated with the preventive work carried on in infant welfare centres and the school health service. Such association might take the form of part-time work in the centres or the acting as consultants for special problems and difficulties.

The development of paediatrics on a regional basis will lead, it is hoped, to a close association between paediatricians working at the centre, i.e. on the staff of the University Institute of Child Health, and those at the periphery in the hospital centres. Interchange of staff for periods, weekly and other regular visits to take part in clinics and case conferences, will all help to prevent the risk of isolation. Voluntary associations, on a regional basis, of paediatricians working in all branches —hospital and child health—are already being developed with the encouragement of the British Paediatric Association.

It is difficult to predict how much private consulting work in paediatrics will continue. Up to a few years ago there were very few whole-time paeditricians on the hospital side except in certain municipal and county council hospitals. The staffing of the preventive services in most cases was becoming, however, more and more on a full-time basis. The development of University Departments and Institutes of Child Health has meant that more full-time paediatricians are now doing a type of work which largely if not entirely excludes private practice. Nevertheless at a children's hospital the majority of the staff at present are arranging to accept service under the Health Act on a sessional basis, leaving some time free for private work. As from July 5 everybody in this country is entitled to the "free" (i.e. as covered by the Act) services of a general practitioner or family doctor. He can secure for them if necessary the domiciliary visit of a consulting paediatrician. All hospitals are open for the reception without payment of patients of whatever income, both in the out-patient department and as in-patients. What this is going to mean in terms of residual private work is not at all certain. For the payment of a fee a child patient can be seen privately at a paediatrician's consulting room ("office") and can be admitted to a private ward or room at a hospital for treatment or an operation for which a fee is charged. The scale of charges for private accommodation is, however, based upon the cost of the hospital beds which has risen greatly in recent years and there is a limit placed on what the specialist can charge as his fees. The child patient in the best chil-

dren's hospitals today receives exactly the same standard of medical and nursing care and feeding whether in a private or a public ward. The reaction of the public—at any rate the middle-class who have hitherto provided the bulk of private consulting work—to the situation cannot yet be gauged.

ALAN MONCRIEFF, Corresponding Editor

SCOTTISH LETTER

Any consideration of the paediatric problems peculiar to Scotland, and the future organization of the Scottish paediatric services, must begin with a brief review of the geographical features and distribution of population in this country. Of a total population of approximately five million, more than one million are living in a single city (Glasgow), and a further half million in Edinburgh and the forty-mile belt separating the two cities. In striking contrast to this densely populated area, the Highlands and Islands, which lie to the North and North West of this urban belt, represent one of the wildest and least accessible areas in Great Britain. Since the Highlands were largely given over to deer forests and sheep farming in the eighteenth century, there has been a steady depopulation of the mountainous areas, which has drained off the more active and enterprising members of the community, either by emigration or removal to the larger cities. The Western Isles comprise more than 500 islands and islets of which only 102 are now inhabited; of their total area of 2,812 square miles only 300 square miles are under cultivation. Thus although the Highlands and Islands represent approximately half the land area of the country, they contain only one sixteenth of the population. For the Highlanders and Islanders that remain, the provision of an adequate medical service, and indeed of schools and all other social services in the more isolated areas, is a very real problem.

The paediatric problems of Scotland are therefore of two completely different types, and are mainly concerned with (1) the mushroom-growth of Glasgow, with all the attendant child health disabilities that overcrowding in a large industrial city in a northern climate implies, and (2) the care of a dwindling population in remote and isolated areas, where the barren character of the land makes subsistence hard and precarious, and where, in the islands, the absence of road and rail facilities render the population dependent on boat and aeroplane for communication with the mainland.

The following sketch map of Scotland, which has been divided according to the hospital regions of the new National Health Service, illustrates the striking differences in population of different areas. Thus the Western Region has a comparable land area but considerably more than ten times the population of the Northern Region, whilst the North Eastern Region, which includes the Orkney and Shetland Islands, extends through more than three degrees of latitude and has a population of only 510,000.

University paediatric centres exist in Glasgow, Edinburgh, Aberdeen, and Dundee (the clinical centre for St. Andrew's University), and there is a well equipped hospital in Inverness on which the hospital services for the Northern Region are based. It will be seen, however, that the transfer of a child to such a centre from the Outer Hebrides or one of the remoter islands will involve a journey by land and sea, which in bad weather may be extremely hazardous. Since many of the islands and inland areas are so mountainous that outlying crofts can barely be reached by automobile and are remote from rail communication, it will be realised that mileage is little index of the difficulties which have to be overcome. Even the use of air ambulances is limited by landing facilities and adverse flying conditions.

More than 30 years before the introduction of the National Health Service on July 5, 1948, it was realised that the State must play a part in subsidising the health service for the Highlands and Islands, and during this time a medical service has been developed which has proved an exceptionally interesting experiment in social medicine. The scheme has been described in more detail by Sir Andrew Davidson (1948), Chief Medical Officer of The Department of Health for Scotland, and it need only be said here that it includes the subsidy of doctors carrying out domiciliary practice amongst a scattered population largely of the smallholder or crofter class; provision of district nurses, whose duties include not only domiciliary nursing but also infant welfare and school medical work; central hospital and consulting facilities; and the provision of transport (including air ambulances) for nurses, doctors, and patients.

On the other end of the scale are the paediatric problems provided by Glasgow, and to a less

extent by Edinburgh and other large burghs. In considering the infant mortality rate in these cities, it must be remembered that Glasgow lies within the same latitude as Labrador, and suffers the double disability of a northern climate and early unplanned industrialisation, whilst Edinburgh was originally built on a mountainous site selected for defence, and contains many occupied dwellings dating from the sixteenth and seventeenth centuries.

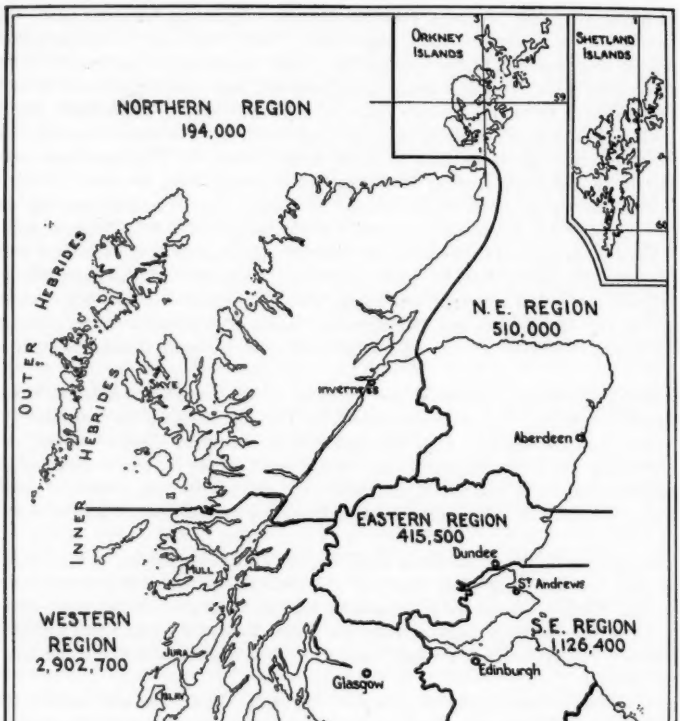


FIG. 1. Scotland, divided into Regions (National Health Service, 1948) showing population and main hospital centres.

Against this background of mountain and slum, industrialisation and early history, and a fierce traditionalism which extends to clothing and diet, must be seen the day to day problems of child health and preventive medicine which it is hoped to discuss in subsequent communications.

Infant Mortality. Towards the end of the last century (1891-5), the infant mortality in Scotland was 126 per 1000 live births, compared with 151 in England and Wales, and 165 in Holland. By 1936-40 the position had become reversed, Scotland having the highest rate (76), England and

Wales 55, and Holland 37. Thus although the infant mortality rate in Scotland had fallen substantially, it had not done so to the same extent as that of her neighbours.

In 1945, the difference between the Scottish infant mortality rate of 56 and that for England and Wales (46) was still considerable, although England had suffered from enemy action and the disruption of war to a greater extent than had Scotland. The causes of this high infant mortality rate are only partially related to climatic conditions, and indeed the most striking difference is observed in the infant mortality rate in Port-Glasgow, Paisley Burgh, and Greenock Burgh, which in 1945 had rates of 78.2, 75.1, and 74.1 respectively, and the rate for the rest of the same County (Renfrew) which has the same climate and an infant mortality rate of 48.2 per 1000 live births. Thus whilst it is not by any means always true that the large cities have a higher infant mortality rate than the adjacent rural areas, it is found that the general rate for the large burghs is substan-

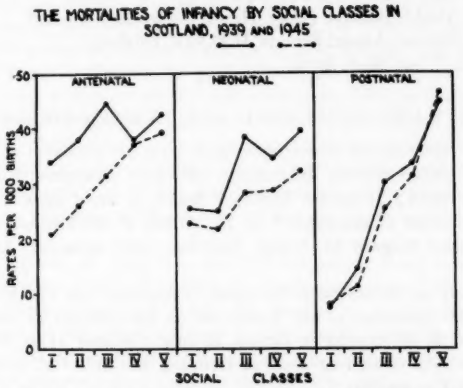


FIG. 2. Antenatal, neonatal, and postnatal mortality rates in 1939 (unbroken line) and 1945 (broken line) by economic class. (After McKinlay, 1948.)

tially higher than that for the counties excluding large burghs (62.0 as compared with 49.2). The significance of this in the planning of the future paediatric services will be discussed at a later date.

Stillbirth Rate. The stillbirth rate, calculated as the number of stillbirths per 1000 births, i.e. live and stillbirths, is classified in Scotland according to economic status and also cause. Whilst the value of certified "cause" will obviously depend to a large extent on the proportion of stillborn infants subjected to postmortem examination, the requirement for certification is likely to lead to more critical assessment of causes of stillbirth as time goes on. Classification by economic status is based on the occupation of the father. Class I includes the professional classes, commissioned officers, higher-salaried business men, and those of independent means; Class III skilled workers, including miners; and Class V unskilled and casual labourers. Class II is intermediary between I and III, and Class IV represents semi-skilled labourers. For practical purposes, Classes I and II are taken to represent the more well-to-do sections of the community, and Classes IV and V the poorest. The status of Class III at any given time depends to a great extent on economic and industrial conditions.

In view of the great stress that has been laid on nutrition as a cause of stillbirth, a comparison of the rates of stillbirth, neonatal (death rate under 1 month) and postnatal death rate (1 to 12 months) in 1939 and 1945 is of particular interest. With the introduction of rationing and the National Milk Scheme, and a high level of full employment, there can be no doubt that there has been a general leveling of nutritional standards in the country between economic classes. The well-to-do get less than before the war and Classes IV and V approach much more nearly to the nutritional standards of Classes I and II than before. When the stillbirth (antenatal mortality) rates are compared, however (Fig. 2), it has been pointed out by McKinlay (1948) that the differences between social classes in 1945 is actually greater and not less than in 1939. The stillbirth rate increases steadily from Class I (where it is substantially lower than before the war) to Class V where

it is practically the same as in 1939. The reason for this is not at once obvious. It has previously been thought that overcrowding was of relatively little importance as compared to nutrition in the causation of stillbirth (Woolf, 1947), but of differences between economic groups this is probably now the greatest. The figures do of course call for further analysis with regard to maternal age and parity, and they are presented simply with the purpose of showing that a levelling of nutritional standards has not in fact produced the levelling of stillbirth rate which might have been expected.

RICHARD W. B. ELLIS, Corresponding Editor

Department of Child Life and Health,
University of Edinburgh.

REFERENCES

Davidson, A. (1948). Bull. Johns Hopkins Hosp., **82**:479.
McKinlay, P. (1948). Health Bulletin (Dept. Health for Scotland), **6**:8.
Registrar General for Scotland, Annual Reports. H.M.S.O., Edinburg.
Woolf, B. (1947). Brit. J. Soc. Med., **1**:73.

U.N.'S CHILDREN'S FUND AIDS GERMAN CHILDREN

The first post-war report by an international agency on the condition of German children was issued recently by the United Nations International Children's Emergency Fund. This report, which was prepared for the Fund's 26-nations Executive Board, is based upon a survey in the French, British, and American zones of occupation* by Dr. Arnold P. Meiklejohn, nutrition expert of the University of Edinburgh; Surgeon M. Keeny, American relief authority; and Dr. Carl E. Raiha, Finnish pediatrician.

The report was made in late spring as the result of requests from the three Zonal Commanders, looking toward possible extension of the Fund's aid to the children in those zones. The Board, acting upon the report at its meeting in Geneva in July, allocated $1,000,000 for a four months' initial program for children in all four zones of Germany, this aid to be available upon the request of the respective Zonal Commanders.

However, the money is not to be used for mass feeding programs, as in other European countries where the Fund is operating, but will be used instead for special health and welfare projects, the reason being that the occupation forces of the American and British zones of Germany have been carrying on a school feeding program for an extended period. Thus, with the exception of the French zones where only a partial school feeding program is undertaken, the German children in the zones surveyed are receiving through the occupation powers relief similar to that which is being provided in 12 other European countries by the United Nations International Children's Emergency Fund. The report of the survey committee paid a tribute to the occupation forces for the job that has been done through mass feeding programs. At the same time a warning was issued that while the German children were "not starving," the circumstances under which they were living were creating grave psychologic difficulties.

The report, while concerned primarily with the condition of children, necessarily covered the larger social group. It states, that while the German people are not starving or severely undernourished, nobody, including the military is satisfied with the situation, and it is conceded that the population is suffering from serious social and psychologic problems. Because of this, the report recommended that UNICEF provide aid for German children, and emphasized that "any help given by UNICEF, if properly interpreted as expressing the goodwill of the United Nations, would be likely to result in psychologic benefits far greater than the purely physical relief given."

* No request was received for a survey of the Soviet Occupation Zone.

BOOK REVIEWS

PSYCHIATRY FOR THE PEDIATRICIAN, Hale Shirley, M.D. $4.50, 435 pages, The Commonwealth Fund, New York, 1948.

Information in this book for the most part is sound and is presented in a clear fashion. It contains some material which, though good, is not particularly needed by the practicing pediatrician, and this tends to make the book too long. It lacks integration and a continuity which would make it much more interesting reading. The approach is primarily that of a psychiatrist and there is a tendency to assume that the pediatrician will have certain psychiatric tools and orientation. For example, the author speaks of the fact that the physical, emotional, and social factors are interrelated and should be considered in evaluating a child, but he does not give the reader a clear understanding of *how* these factors operate and *how* they are interrelated. He gives the pediatrician some good material, but there is little help as to how it can be used in practice. The phrases, "Appropriate treatment should be instituted"; "Educate the parents," "Reassure the parents" are used frequently, but going another step and giving the pediatrician some suggestions as to how this commendable advice could be carried out would make the book a much more real and valuable communication.

Case histories are used to illustrate certain points, but there is the impression of seeing children in cross-section rather than longitudinally and as "cases" rather than as children in varying stages of development with problems and with parents who have problems. One does not, for the most part, recognize these *people* in the book, and for a book of this sort to have real meaning to the pediatrician, that is important.

There is too little emphasis on what the child and his parents think, enjoy, do, feel, and say about the various situations for which the pediatrician is consulted and *why* they feel, etc. as they do. Lip service is paid the interpersonal relationships, but there is too little development of the subject and too little explanation of the physician's part in the picture. Unfortunately, the author in an attempt at thoroughness has at times presented material which should not have been included or which should have been presented in a different manner. For example, on page 109 among the remedies for enuresis, urethral dilatation is mentioned as a procedure which "has been recommended." The reader might infer that the author accepts this practice because there are no qualifying statements to the contrary. Shirley might have done a real service to children by pointing out that urologic investigation in instances of enuresis must be done only where there are clearcut indications and only after psychological appraisal has been included in the study of the child. This reviewer believes the author errs in a similar fashion when he mentions also on page 109 that apparatuses have been devised "to waken a child when he wets the bed." Thus one sees in the chapter on enuresis, a mixture of child guidance which on the one hand follows a kindly, sympathetic and understanding philosophy, yet antithetically seems to give tacit approval to practices of child study and child rearing which are impersonal and mechanistic, and which on occasion may even be psychologically traumatic.

Lastly, there is a failure to impart to the reader the feeling that in understanding the growing and developing total child *as a person* and in helping him and his often bewildered parents to realize and accept his own individual optimum development, the pediatrician has an opportunity not only to make an invaluable contribution to people, but also to gain great personal satisfaction and gratification from the practice of pediatrics.

SALLY ANN PROVENCE

AN ACCOUNT OF THE WEATHER AND DISEASES OF SOUTH CAROLINA. By Lionel Chalmers, M.D. of Charles-Town, South Carolina. London, Edward and Charles Dilly, 1776. (Facsimile selections, Richmond, 1948).

Lionel Chalmers of Charleston, South Carolina, came nearer to being a pediatric specialist than any other physician of the American colonial period. Although Douglass had written on scarlet fever, Bard on diphtheria, and Rush on infantile diarrhea, Chalmers not only published his observations on these diseases but also covered a much wider range of pediatric subjects. He appears to have been among the first in this country to appreciate that rickets did not include all bony deformities,

that "nine-day fits" of infants was the same disease as tetanus of adults, and that thrush was not usually a primary cause of death. He also wrote on infant feeding, weaning, teething, worms, convulsions, impetigo and obstructive laryngitis. He was most original and perhaps at his best in his descriptions of whooping cough and mumps.

It was a fortunate decision when the South Carolina Medical Society selected excerpts from "The Weather and Diseases" and a biographical introduction by Dr. Joseph I. Waring as a fitting souvenir of its Centennial. Mead Johnson and Company, having faithfully reproduced these selections in facsimile on an excellent grade of paper, now generously present American pediatricians with this work of lasting value. This is really a souvenir that should be read and treasured. In fact, it is compulsory reading for every pediatrician who has any regard for the cultural aspects of his profession.

ERNEST CAULFIELD

THE POSTNATAL DEVELOPMENT OF THE HUMAN CEREBRAL CORTEX. VOLUME III; THE CORTEX OF THE THREE-MONTH INFANT. By J. deRoy Conel, Harvard University Press, Cambridge, Mass. 1947.

This is the third volume of Dr. Conel's unique monographic series which extends his meticulous microscopic study of the development of the human cortex to three months of age. It presents in detail the histologic criteria of development by which comparison may be made of brains of the same or different ages or of various areas within the cortex of one brain. The criteria are: 1. width of entire cortex and of each horizontal layer; 2. number of cells; 3. size of nerve cells; 4. condition of the chromophil substance; 5. neurofibrils; 6. size, compactness of structure (including varicosities), and length of processes of nerve cells; 7. pedunculated bulbs; 8. size and quantity of exogenous fibers; and 9. state of myelination. The manifestations of growth and development of the cerebral cortex by these criteria correlate with observations on the progression of voluntary activity in infants. The implications of such work to correlation of histologic structure with physiologic function not only in growth but also in disease are too obvious to require comment. Certainly to pathologists, neuro-anatomists and neurologists Dr. Conel's studies as revealed in the three volumes now published present a comparative anatomy of the cerebral cortex that will be invaluable as a standard of reference. The excellence of the reproduction, as well as the original execution, of the 220 figures deserves comment.

ALLAN M. BUTLER

MUSCLE TESTING, Lucille Daniels, M.A., Marian Williams, M.A., and Catherine Worthingham, M.A. $3.00, 188 pages, 349 diagrammatic line drawings. W. B. Saunders Co., Philadelphia and London, 1947.

This book presents a technic for manual muscle examination and evaluation of muscle strength. It gives in detail information on muscle topography, muscle function, joint range, and nerve distribution by means of 349 line drawings made from photographs and diagrams. The work has been done with aid and supervision from the National Foundation for Infantile Paralysis. It includes the charts for muscle examination supplied by the National Foundation. The text is limited to notes for each drawing and diagram. Miss Daniels and Miss Williams are respectively Associate Professor and Assistant Professor of Physical Therapy, Stanford University. Miss Worthingham is Director of Professional Education, the National Foundation for Infantile Paralysis, Inc.,

The book is of prime importance to pediatricians in determining degrees of muscular weakness and providing a basis on which muscle re-education can be prescribed by retesting. An indication of the rate and amount of the improvement and the results of treatment procedures can be evaluated.

HUGH MCCULLOCH

LETTERS TO THE EDITOR

Re: Congenital Alveolar Dysplasia of the Lungs by H. Edward MacMahon, Pediatrics **2**:43, 1948.

August 24, 1948

To the Editor:

No organ in the body has been the object of a greater number of erroneous descriptions and interpretations of normal and abnormal processes than has the lung and it seems unfortunate that your journal has been guilty of adding to the welter of misstatements about this organ. Simultaneously in the July issue of the AMERICAN JOURNAL OF PATHOLOGY and in PEDIATRICS Dr. H. Edward MacMahon has described a condition under the title "Congenital Alveolar Dysplasia of the Lungs" which he has found in many infants. He believes it is a congenital malformation often incompatible with life, resulting from the failure of alveoli to develop normally. He describes a clinical picture in which the infant is usually normal at birth, becomes progressively dyspneic and cyanotic and often dies of respiratory failure in 36 to 48 hours. Postmortem examination reveals red purple lungs that are of increased size and weight, that contain no visible air and sink in water. In relation to microscopic examination, he states, "There are too few alveoli and there is too much interstitial tissue." "The histologic structure of the lung bears a resemblance to the pattern in a three to four-month-old fetus." "In its simplest form the histologic picture resembles the pulmonary pattern that one finds during the fourth and fifth month of intrauterine life." "This picture of a large lung composed of an excess of primitive but highly vascularized interalveolar mesenchymal tissue, a diminished number of alveoli and many overdistended alveolar ducts constitutes the essential findings in congenital alveolar dysplasia."

Dr. MacMahon was unfortunate in not having consultants who were familiar with the development of the fetal lung and with the full range of disturbances that can be found in the lung of the newborn infant. The pictures of the lungs of a 12, 16 and 22 week fetus which he states resemble those of alveolar dysplasia are, indeed, pictures of normal lungs at these ages but any resemblance to the pathologic process he is describing results almost entirely from the inability of photomicrographs to show details of cellular structure. Of the 16-week fetus he states "alveoli are small and evenly distributed" and of the 22-week fetus "solid nests of cells appear to be budding from the alveoli." These statements are both in error for the lung of the 16-week fetus ordinarily contains no alveoli, and the structures from which "solid nests of cells" arise are not alveoli.

The lungs of infants with diaphragmatic hernias and anencephalic monsters with a complete spinal rhachischisis, causing a diminution of space within the chest, will actually shown abnormality in pulmonary development consisting principally of an excessive number of bronchi and bronchioles in relation to the more distal portions of the pulmonary tree. We have ordinarily called these simply "pulmonary hypoplasia," but they might quite correctly be called a congenital alveolar dysplasia.

The picture described by Dr. MacMahon, however, is not a malformation, and is actually only one variety of atelectasis. He states that this condition will have been seen but not recognized by anyone doing autopsies on newborn children and that it will have been mistaken for atelectasis. It will not have been "mistaken" for atelectasis because that is what it is. It has been the subject of intensive study in the laboratory of the Chicago Lying-in Hospital because it is the second largest cause of death in that institution. In the last year we have observed 12 infants with this condition; if it were a malformation 56% of our total infant deaths would be from some variety of malformation.

We have called this condition a "resorption atelectasis" to differentiate it from the findings in a fetus who has never breathed and from the compression and flattening which will be produced by a tumor as shown in one of Dr. MacMahon's photographs. As Dr. MacMahon pointed out the proximal air spaces in many such lungs are overdistended and many are lined by a granular or homgeneous layer of eosinophilic material. The intervening areas described by him as mesenchyme abnormally rich in capillaries and devoid of alveoli are actually areas in which capillaries are intensely engorged with blood and the walls of the alveoli and alveolar ducts are in such complete approximation that apparently solid highly vascular appearing areas are produced. These cases are easily recognized

grossly by the liverlike color and consistency of the lungs and the apparent increase in size. One has only to tie off one lung and inject the other intratracheally with Zenkers or other fixing fluid to convince oneself that these lungs are actually normally developed. The uninjected lung will show a picture identical to that described by Dr. MacMahon as a malformation of the lung; the injected lung will show the pattern found normally in utero which is produced by the even distribution of fluid within the pulmonary system. Intratracheal injection of fluid will open up the collapsed air spaces and will show the true nature of the apparently solid mesenchyme. The introduction of air will only cause more hyperdistention of the proximal portions and greater collapse of the more distal portions.

We hope Dr. MacMahon will continue his investigation of infants with this form of lung pathology for in our experience it is an extremely important cause of death among infants weighing from 1800 to 2500 gms. It also occurs in a few at term, particularly if they are delivered by Cesarean section, as were two of the three infants for whom Dr. MacMahon gives case histories. We hope he will not be content to dismiss these infants as being hopelessly malformed but will attempt to find a way of preventing the development of such pulmonary changes.

Sincerely yours,

(Signed) EDITH L. POTTER, M.D.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, M.D., *Contributing Editor*

INCIDENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES

NUMBER OF REPORTED CASES OF 9 COMMUNICABLE DISEASES IN THE UNITED STATES DURING THE 4-WEEK PERIOD JUNE 20–JULY 17, 1948, THE NUMBER FOR THE CORRESPONDING PERIOD IN 1947, AND THE MEDIAN NUMBER OF CASES REPORTED FOR THE CORRESPONDING PERIOD, 1943–47

Division	Current period	1947	5-year median	Current period	1947	5-year median	Current period	1947	5-year median
	Diphtheria			Influenza[1]			Measles		
United States	369	563	623	2,333	2,229	2,229	45,336	17,946	21,021
New England	25	32	25	9	8	8	4,584	2,909	2,909
Middle Atlantic	51	108	102	8	21	21	15,012	4,121	4,121
East North Central	53	58	100	23	56	61	10,086	5,722	5,722
West North Central	29	59	62	36	7	15	842	1,881	1,102
South Atlantic	62	86	94	1,013	936	706	3,697	1,225	1,719
East South Central	37	42	45	46	55	65	471	341	341
West South Central	52	79	120	1,052	946	1,156	2,334	679	943
Mountain	26	27	42	113	160	166	2,145	531	723
Pacific	34	72	100	33	40	54	6,165	537	3,191
	Meningococcus meningitis			Poliomyelitis			Scarlet fever		
United States	202	216	502	1,901	369	678	2,951	3,156	4,602
New England	9	9	25	12	15	15	545	272	622
Middle Atlantic	31	47	98	86	41	67	660	845	1,237
East North Central	44	43	114	138	47	50	879	983	1,182
West North Central	20	23	34	116	41	30	153	269	284
South Atlantic	36	34	60	638	41	105	189	180	296
East South Central	22	18	48	78	8	87	98	87	108
West South Central	25	24	50	380	31	187	71	98	152
Mountain	1	2	10	44	22	22	92	135	222
Pacific	14	16	58	409	123	100	264	287	502
	Smallpox			Typhoid and paratyphoid fever			Whooping cough		
United States	1	5	19	377	350	498	4,665	14,204	10,251
New England	0	0	0	14	13	20	196	865	784
Middle Atlantic	0	0	0	37	31	40	702	2,442	2,442
East North Central	0	1	6	44	42	53	552	2,725	1,789
West North Central	1	3	3	14	12	20	209	773	648
South Atlantic	0	0	0	71	54	118	1,150	2,459	1,987
East South Central	0	0	1	59	38	69	287	590	590
West South Central	0	0	2	89	110	127	976	2,841	1,096
Mountain	0	1	1	10	12	15	274	539	490
Pacific	0	0	0	39	38	19	319	970	970

[1] New York, North Carolina, and Pennsylvania excluded; New York City and Philadelphia included.

For total United States	Cases for each week of current period				Following week
	1st	2nd	3rd	4th	
Diphtheria	98	86	96	89	
Influenza	631	463	619	620	
Measles	15,594	12,488	9,618	7,636	
Meningococcus meningitis	55	50	39	58	
Poliomyelitis	309	362	513	717	
Scarlet fever	1,066	781	608	496	
Smallpox	0	0	0	1	
Typhoid and paratyphoid fever	89	98	90	100	
Whooping cough	1,297	1,067	1,107	1,194	

NUMBER OF REPORTED CASES OF 9 COMMUNICABLE DISEASES IN THE UNITED STATES DURING THE 4-WEEK PERIOD JULY 18–AUGUST 14, 1948, THE NUMBER FOR THE CORRESPONDING PERIOD IN 1947, AND THE MEDIAN NUMBER OF CASES REPORTED FOR THE CORRESPONDING PERIOD, 1943–47

Division	Current period	1947	5-year median	Current period	1947	5-year median	Current period	1947	5-year median
	Diphtheria			Influenza[1]			Measles		
United States	490	526	713	2,675	2,095	2,095	13,474	6,935	6,935
New England	24	23	19	4	5	2	1,593	696	696
Middle Atlantic	43	86	58	10	17	17	3,878	1,560	1,560
East North Central	42	54	83	26	22	56	2,885	2,485	2,439
West North Central	29	68	59	13	11	15	293	637	300
South Atlantic	155	76	136	1,321	966	726	1,073	521	528
East South Central	53	57	70	51	110	103	218	96	96
West South Central	81	92	135	1,117	829	842	890	367	367
Mountain	23	18	41	93	109	110	814	251	455
Pacific	40	52	81	40	26	26	1,830	322	1,001
	Meningococcus meningitis			Poliomyelitis			Scarlet fever		
United States	210	201	428	4,848	825	1,907	1,501	1,927	2,888
New England	15	9	24	85	70	86	178	159	261
Middle Atlantic	44	35	81	444	128	252	287	416	492
East North Central	34	35	81	639	173	210	414	548	586
West North Central	18	13	38	569	130	130	105	154	234
South Atlantic	27	36	52	1,345	69	183	150	178	313
East South Central	30	17	41	236	32	131	87	86	139
West South Central	17	27	40	493	56	272	77	78	125
Mountain	6	11	11	136	52	67	54	78	157
Pacific	19	18	50	901	115	121	149	230	422
	Smallpox			Typhoid and paratyphoid fever			Whooping cough		
United States	4	4	11	401	510	625	4,112	14,659	11,802
New England	0	0	0	13	20	26	230	925	919
Middle Atlantic	0	0	0	51	50	50	890	2,646	2,614
East North Central	1	0	3	45	48	73	686	3,933	2,722
West North Central	1	1	3	17	24	25	180	1,067	609
South Atlantic	0	1	0	98	95	140	803	1,993	1,993
East South Central	1	0	1	55	59	100	204	534	534
West South Central	0	1	2	88	103	158	551	2,068	918
Mountain	1	1	1	11	23	26	216	588	584
Pacific	0	0	0	23	88	33	352	905	905

[1] New York, North Carolina, and Pennsylvania excluded; New York City and Philadelphia included.

For total United States	Cases for each week of current period				Following week	For total United States	Cases for each week of current period				Following week
	1st	2nd	3rd	4th			1st	2nd	3rd	4th	
Diphtheria	107	113	126	144		Poliomyelitis	983	1,215	1,239	1,411	
Influenza	602	691	691	691		Scarlet fever	435	395	316	355	
Measles	5,128	3,789	2,584	1,973		Smallpox	1	1	1	1	
Meningococcus meningitis	54	54	57	45		Typhoid and paratyphoid fever	93	93	107	108	
						Whopping cough	969	1,167	974	1,002	